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Comparison of Opioid Utilization With Different Perioperative Pain Protocols After Scheduled Cesarean Delivery

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Abstract

Objective: Cesarean delivery pain management protocols involving pre-operative gabapentin and acetaminophen, or those specifying wound infiltration with liposomal bupivacaine, may decrease postoperative opioid utilization compared to protocols involving only neuraxial preservative-free (PF) morphine. We compared postoperative opioid consumption after scheduled cesarean deliveries among these three methods of pain management.

Methods: Patients undergoing cesarean delivery with neuraxial anesthesia from January 2016 to July 2017 in our database were sorted into one of three groups: those who received gabapentin preoperatively and IV acetaminophen after fascia closure (A), those who received liposomal bupivacaine infiltrated into the wound (E), and those who received PF morphine additive as spinal or epidural anesthesia (S). Each patient's postoperative morphine equivalent units (MEUs) were calculated. Multiple regression analysis with a mixed-effects model determined the independent effects of treatment group, type of neuraxial anesthesia, age, race, surgeon, gravidity, and cesarean delivery status (primary/repeat).

Results: A total of 1411 patients met the inclusion criteria. Groups differed in gravidity, race, cesarean delivery status, and anesthesia mode. Independent of those differences, MEU use differed (p <0.0001), with group A < group S < group E (all comparisons p <0.05).

Conclusion: Preoperative oral gabapentin and intraoperative acetaminophen were associated with decreased perioperative opioid consumption compared to neuraxial opioids or wound infiltration with liposomal bupivacaine. This observational data warrants future similar, follow-up randomized, blinded studies.

Categories: Obstetrics/Gynecology, Anesthesiology
Keywords: cesarean delivery, gabapentin, liposomal bupivacaine, obstetrical analgesia, obstetrical anesthesia, postoperative pain

Introduction

Globally, about 21% of patients undergo delivery via cesarean delivery, with rates increasing worldwide [1]. Pain, one of the most common postpartum complaints after cesarean delivery, remains undertreated, and its severity is often underestimated [2]. In a large survey of childbearing patients performed in the United States, 58% of women undergoing cesarean delivery reported postpartum incisional pain while 19% cited pain as a major problem [3]. Post-cesarean delivery pain impacts the immediate postpartum period as well as recovery after discharge. Pain after delivery impairs mobilization, increasing the risk of venous thromboembolism. Shallow breathing and splinting lead to atelectasis and pneumonia. These sequelae prevent or curtail breastfeeding [4,5].

Enhanced recovery after surgery (ERAS) protocols, adapted for cesarean delivery, can improve postoperative recovery and limit pain. These protocols decrease opioid consumption both during hospital stay and upon discharge [6]. Opioids provide effective analgesia at rest, but not often with activity [7]. Multimodal pain management reduces or eliminates opioid utilization, with the goals of early ambulation and return to normal activity. A typical ERAS postpartum pain protocol might include NSAIDs (i.e., ketorolac IV), acetaminophen every 6 hours by schedule, supplemental oral and/or IV opioids as needed, gabapentin, local wound infiltration, and/or peripheral nerve blocks. Perioperatively, regional anesthesia with intrathecal morphine augments postoperative analgesia [8]. However, intrathecal morphine dosing can vary based on provider preference and institutional guidelines, and side effects such as nausea, vomiting, and pruritus occur with higher doses. Local anesthetic wound injection and/or fascial plane blocks substitute for intrathecal opioids [2].

Studies evaluating ERAS and alternative pain protocols are underpowered, highly heterogeneous, and often

confound pre-, peri-, and postoperative interventions. This post hoc analysis compares three perioperative pain protocols in a community-based hospital system for the ability to reduce postpartum opioid use: wound injection of Exparel® (bupivacaine liposome injectable suspension) at closure, perioperative acetaminophen and gabapentin, and preservative-free (PF) morphine injected with spinal or epidural anesthesia.

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Materials And Methods

Study design

With approval from the Main Line Hospitals Institutional Review Board (F/N-R18-3799BLP), we extracted de-identified records from our institutional databases of patients who underwent cesarean delivery between January 2016 and July 2017. During this period, patients received one of three pain management protocols, chosen by their caregivers in an unmasked, non-randomized fashion. Group E received an injection into the surgical wound at the time of skin closure of a solution of liposomal bupivacaine formed by diluting 20 mL of 1.3% liposomal bupivacaine into 60 mL total volume. Group A received acetaminophen 1 g IV preoperatively followed by 975 mg PO every 6 hours after operation. They also received 600 mg gabapentin PO preoperatively. Group S received 0.2 mg intrathecal PF morphine or 2.0 mg epidural PF morphine, depending on the choice of regional anesthesia technique. Those in groups E or A did not receive neuraxial PF morphine. Those in groups E or S did not receive acetaminophen or gabapentin prior to or during cesarean delivery. All groups received a standard postoperative pain regimen protocol of alternating PO acetaminophen and IV ketorolac. Patients who received an epidural had this removed prior to discharge from the post-anesthesia care unit (PACU).

Data collection

Data collected included demographics (height, weight, age, race), gestational age, gravidity, primary or repeat cesarean delivery status, postpartum pain management group (E, A, or S), name of obstetrician, and opioid consumption starting at discharge from the PACU until discharge from the hospital. Standard morphine milligram equivalent conversion factors were used to convert all opioid doses to morphine equivalent units (MEU) [9]. All opioids administered post-PACU discharge, including IV and PO opioids, were included in the MEU calculations.

Selection criteria

The analysis included all patients who underwent cesarean delivery across the 4 community hospitals in our healthcare system. The analysis excluded patients who received any anesthetic or combination of anesthetics other than spinal or epidural anesthesia (i.e. general anesthesia). Patients who received a pain protocol differing from the three protocols mentioned in our study design were also excluded. We also excluded patients who underwent complications that may have impacted pain management, including subsequent procedures post-cesarean section, postpartum hemorrhage, and seizures. Patients who received naloxone or other medications that would impact opioid usage were also excluded from analysis.

Statistical analysis

Patient records meeting the selection criteria underwent comparison of selected demographic variables by postoperative pain management group (A, E, or S) as follows: analysis of variance for age, and likelihood ratio (chi-square test) for each of gravidity, race, repeat cesarean status, and primary anesthesia modality. Any gravidity greater than seven was represented as seven. We grouped patients into five categories of race (African American, Asian, Caucasian, other, and not recorded) and four categories of primary anesthetic (epidural, spinal, combined spinal epidural, not recorded). For brevity, results are presented as mean and standard deviation for age, gravidity, and MEUs, and as percent of patients for African Americans, repeat cesarean delivery, and spinal anesthesia.

Analysis of the primary outcome variable, total MEUs consumed postoperatively, employed multiple regression analysis using a mixed-effects model with MEUs as the dependent variable using predictors of group, age, race, gravidity, cesarean delivery status (primary or repeat), type of anesthesia (spinal or epidural), and obstetrician name. Separately, a sensitivity analysis employed simple one-way analysis of variance followed by Tukey's test for pairwise MEUs comparison.

We pre-specified a 15% reduction in postoperative opioid use in either group E or group A compared to that in group S as a clinically relevant improvement. Based on an expected 50 MEUs for both the mean and standard deviation, and ~1000 records over the 19-month period, the analysis had ~95% power to detect this clinically relevant difference.

Results

The database yielded 1,515 patients for review, of whom 104 met exclusion criteria, as detailed in the

CONSORT diagram in Figure 1. Of the remaining 1,411 patients, 630 received the pain management protocol for group S, 508 received group A, and 273 received group E.

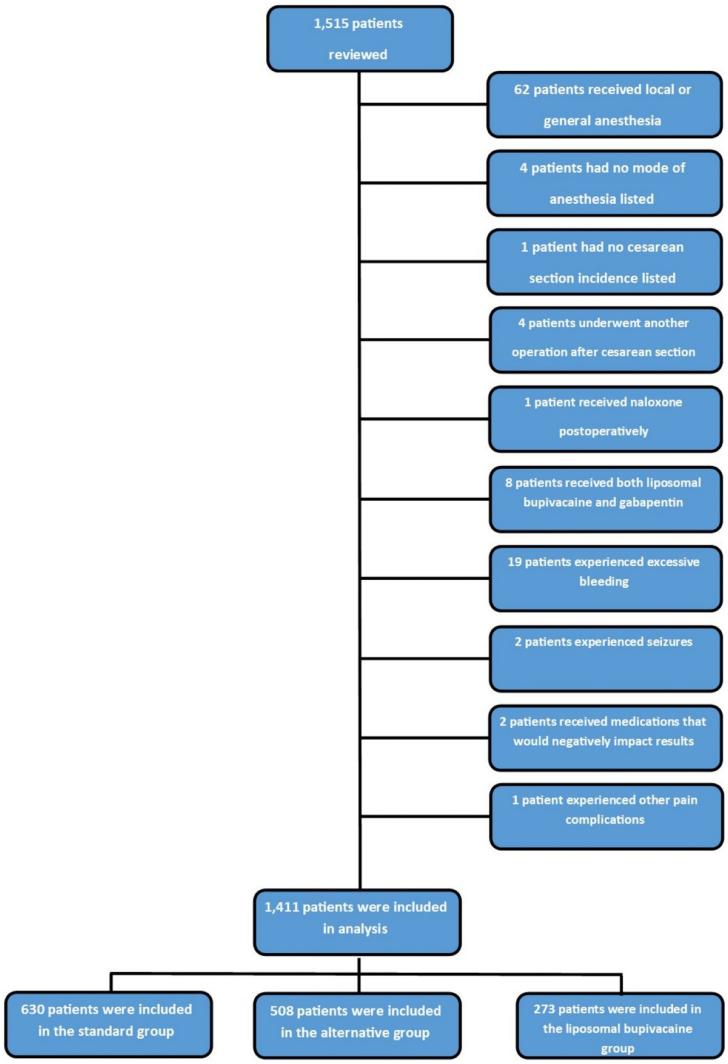


FIGURE 1: CONSORT diagram displaying the disposition of patients

Groups differed in age, race, gravidity, prior cesarean delivery status, and anesthesia mode (Table 1). MEUs significantly differed among groups (p <0.0001) after accounting for the above differences. Compared to Group S, Group A received 15.3±3.56 (SE) fewer MEUs on average (p <0.0001), while Group E received 49.8±4.56 MEUs more than Group S (p<0.0001). Table 1 displays the individual MEU data.

	Group A	Group E	Group S	Test statistic	*p*-value
N	508	273	630	-	-
Age (years)	32 + 4.9	33 + 3.9	32 + 4.9	F=12.6	p <0.0001
Gravidity	2.73 + 1.66	2.37 + 1.45	2.38 + 1.60	$\chi^2(12)=35.1$	p =0.0005
% African American	30	6.2	25	$\chi^2(8)=80.9$	p <0.0001
% repeat C-delivery	56	44	40	$\chi^2(2)=28.4$	p <0.0001
% spinal anesthesia	69	79	45	$\chi^2(6)=155.5$	p <0.0001
MEUs	33.7 + 53.2	94.5 + 63.5	47.4 + 60.7	F=94.17	p <0.0001

TABLE 1: Demographics and result summary statistics

Analysis of variance provided age and MEU F-statistics. Chi-square statistic values are likelihood ratios. Mean ± SD summarize age, gravidity, and MEUs.

Group A: acetaminophen/gabapentin group. Group E: liposomal bupivacaine group. Group S: intrathecal or epidural morphine group.

MEUs: morphine equivalent units; C-delivery: cesarean delivery; NS: not significant.

Opioid use decreased with age by 1.06 MEUs per year (p=0.0052), and with gravidity by 3.89 MEUs per pregnancy (p =0.003). Race, prior cesarean delivery status, type of neuraxial anesthesia, and obstetrician identity did not impact opioid use.

Discussion

This retrospective analysis of opioid consumption using three perioperative pain protocols during cesarean delivery reveals a clinically and statistically significant reduction in opioid use associated with a perioperative regimen of acetaminophen and gabapentin compared to neuraxial PF morphine. Furthermore, it demonstrates a marked association with higher postoperative opioid consumption and wound injection of liposomal bupivacaine.

Gabapentin is an FDA Category C drug and may carry risk when used in pregnancy. However, data attest to its safety following a single oral dose before delivery, as multiple trials showed no difference in neonatal outcomes compared to placebo [10-12]. Lactmed, a database endorsed by the American Academy of Pediatrics that lists drugs and dietary supplements that may affect breastfeeding, notes that maternal doses of gabapentin up to 2.1 g daily produce relatively low levels in infant serum, and that a single oral dose of 600 mg prior to Cesarean delivery appeared to have no effect on breastfeeding initiation [13]. Gabapentin is commonly used in ERAS protocols in non-obstetric surgery. Studies have shown its benefit in decreasing postoperative pain scores, opioid consumption, and postoperative nausea and vomiting after abdominal surgery [14]. There has been interest in the use of gabapentin perioperatively for cesarean deliveries. A meta-analysis of 645 patients involved in placebo-controlled trials showed that patients who received a single 600mg oral dose of gabapentin preoperatively had significantly lower pain scores, but there was no difference in the use of supplemental opioids [15]. Our data adds to the growing body of evidence that supports its use in patients undergoing scheduled cesarean delivery.

Wound infiltration of local anesthetics and regional nerve blocks serve as adjuncts to a perioperative pain control protocol. They are usually simple to administer and do not significantly lengthen procedure time. Bupivacaine remains the preferred local anesthetic because small amounts enter breast milk [16]. A meta-analysis of 8730 participants demonstrated a reduced opioid consumption post-cesarean delivery associated with local or regional block, compared to placebo [17]. Wound infiltration, however, was amongst the least beneficial injection sites. We did not study local anesthesia used for nerve block, e.g., in the transversus abdominus plane. Our data for liposomal bupivacaine apply only to its injection into the wound. Differences in infiltration techniques by different providers may have contributed to the liposomal bupivacaine protocol's marked inferiority. While wound infiltration with bupivacaine may help decrease incisional site pain, our data suggest that if neuraxial morphine cannot be used, better methods exist to reduce postoperative pain.

As study participants were not randomized, we identified multiple possible confounders that led to

differences in the treatment groups outlined in Table *1*. These confounders, however, do not always explain the significant difference noted in MEUs among the treatment groups. Participant age was significantly higher in group E, where participants were about one year older than in groups A and S. Our regression results indicate an effect of age with a negative coefficient. It is the third most significant factor after treatment group and gravidity. Group E, with the highest average age, had higher MEUs despite the negative effect of age. We therefore conclude that the statistical difference in group ages does not explain the higher MEUs in group E and may be limiting that increased value. This further strengthens our conclusion regarding the association of increased postoperative opioid use with the liposomal bupivacaine regimen.

This investigation is limited by its retrospective nature. Although the analysis did correct for several identified group differences, factors not recognized or accounted for in the analysis could produce systematic bias affecting opioid consumption. As the study participants were not randomized, we also acknowledge a high risk of selection bias, which could have impacted results. As caregivers selected which perioperative pain protocols their patients received, there were likely confounders including provider preference, patients' baseline pain tolerance, and prior patient opioid exposure that could have impacted protocol selection. We additionally recognize the heterogeneity between treatment regimens. Group A, which had the lowest opioid use, was the only group to receive both acetaminophen and gabapentin. It is therefore unclear which medication had a greater effect on decreasing opioid use. We additionally did not assess for analgesia side effects. While gabapentin is typically well tolerated, side effects can include dizziness and sedation [14]. The benefit of added analgesia and decreased opioid use must be balanced against possible adverse reactions. Further trials on the addition of gabapentin to perioperative cesarean delivery pain regimens are warranted. This study was conducted in one hospital system comprising four community hospitals in one small geographic region. Generalizability of the study is therefore limited. This analysis, therefore, yields associations only; it cannot infer causation, which could be accomplished from a prospective, randomized trial.

Conclusions

This investigation showed an association between reduced levels of opioid consumption after cesarean delivery in patients who received gabapentin preoperatively along with perioperative acetaminophen, compared to patients who received neuraxial PF morphine or subcutaneous infiltration of liposomal bupivacaine. Wound injection of liposomal bupivacaine for postpartum analgesia was accompanied by the greatest use of supplemental opioids in the postpartum period in our population. Our results highlight the benefit of applying ERAS guidelines to obstetric surgery. Our results also identify a reasonable and effective perioperative pain regimen in patients who are unable or unwilling to receive intrathecal morphine. Randomized controlled trials are needed to assess these pain protocols and could further provide key insight into improving postoperative pain for the obstetric population.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Acquisition, analysis, or interpretation of data: Katarina Smigoc, Jay Horrow, Dmitri Chamchad

Drafting of the manuscript: Katarina Smigoc, Dmitri Chamchad

Critical review of the manuscript for important intellectual content: Jay Horrow

Concept and design: Dmitri Chamchad

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Main Line Hospitals Institutional Review Board issued approval F/N-R18-3799BLP. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** Jay Horrow declare(s) employment from Bristol Myers Squibb. Dr. Jay Horrow is a former employee of Bristol Myers Squibb. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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