Evaluating the Preemptive Use of Ofirmev to Address Post-Cesarean Pain

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Abstract

Uncontrolled postpartum pain has been linked to increased opioid use, increased risk for opioid dependency, depression, and the development of persistent pain (Bateman et al., 2016). The purpose of this project is to assess the use of a preemptive dose of Ofirmev (Tylenol, acetaminophen, paracetamol) 1,000 mg IV in decreasing post-cesarean pain and consequently opioid usage within the first 24-hour postoperative period. This project will evaluate documented pain scores charted in the EPIC charting system by the obstetrics nurses at Hendricks Regional Health. The 24-hour postoperative pain scores of cesarean patients who received acetaminophen before cesarean section will be compared to those who did not receive acetaminophen. Reducing post-cesarean pain scores and opioid usage within the first 24-hours may reduce the risk of opioid dependency, persistent pain, and depression.

Keywords: preemptive, post-cesarean, Ofirmev, Tylenol, acetaminophen, paracetamol, EPIC charting system

Introduction

This project is submitted to Marian University Leighton School of Nursing faculty as partial fulfillment of degree requirements for the Doctor of Nursing Practice, Anesthesia track. Cesarean delivery is the most common inpatient surgical procedure among women in the United States, affecting 1.4 million women annually (Holland, Sudhof & Zera, 2020). The national cesarean rate for 2015 was 32% of all births (US National Center, 2017). Despite the standard use of neuraxial (spinal) anesthesia/analgesia intraoperatively, pain is one of the most commonly reported problems after cesarean section (The American College of Obstetricians and Gynecologists [ACOG], 2018). The American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine (SMFM), recommend maximizing the use

of multimodal non-opioid analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen when feasible and appropriate (Batemen et al., 2016).

Background

Postoperative pain is best treated preemptively by using multimodal analgesic (MMA) techniques (Carvalho & Butwick, 2017). With the expanding interest in investigating the incidence of post-cesarean pain and global increase in opioid dependency, the ACOG is recommending that a three-tiered MMA approach comparable to the one created by the World Health Organization (WHO) in 1986 to treat cancer pain be considered in the pain management of post-cesarean patients (The American College, 2018). The WHO analgesic ladder calls for a multilayered approach to pain treatment in which opioids are secondary and not primary; they are not restricted but instead used only when necessary. This stepwise regimen allows for an opioid-sparring approach by preemptively treating pain with first-line drugs like acetaminophen.

The optimal approach to pain management in the post-cesarean population remains a topic of ongoing debate despite these recommendations set by the ACOG and SMFM to decrease post-cesarean opioid use. Data regarding the use of a detailed, stepwise, pain protocol in the post-cesarean population is absent. However, there is a significant amount of research utilizing non-opioid analgesics, such as acetaminophen, as first-line adjuncts in relieving pain while diminishing opioid usage in this population, which will be the focus of this project.

Problem Statement

Post-cesarean women are experiencing increasing postpartum pain levels, exposing them to a higher risk for opioid dependency, depression, and the development of persistent pain (Bateman et al., 2016). Current suggestions from the ACOG and the SMFM include neuraxial analgesia and non-opioid adjunctive medication as first-line agents, with oral (PO) and parenteral

(IV) opioids reserved for breakthrough pain (ACOG, 2018). This project addresses this problem by evaluating patients' pain scores, some of whom received a non-opioid, adjunctive, first-line agent (Ofirmev 1,000 mg IV) versus those who did not receive the intervention.

Organizational "Gap" Analysis of Project Site

Anesthesia providers at Hendricks Regional Health do not have a standardized way to treat post-cesarean pain. Consequently, some patients are experiencing high levels of pain, frequent occurrences of breakthrough pain, or moderate to high pain at the time of discharge, which results in higher consumption of narcotics during their inpatient stay and upon discharge. This phenomenon places post-cesarean patients at greater risk for persistent or chronic pain and opioid misuse.

Review of the Literature

The clinical question PICO (population, intervention, comparison, and outcome) guiding the search for evidence is as follows: In patients undergoing elective cesarean surgery at Hendricks Regional Health Hospital, how does the use of preoperative Ofirmev 1,000 mg, compared with no preoperative dosing affect the incidence of post-cesarean pain during the first 24-hours postpartum?

A systematic literature search was performed using the following databases (2015 to 2020): PubMed, CINAHL, and Google Scholar. The following keywords, key strings, and mesh terms were used separately or in combination: *Ofirmev, Acetaminophen, Paracetamol, multimodal analgesia, cesarean section, c-section, post-surgical pain, cesarean section /adverse effects, pain management, practice guidelines, obstetric anesthesia, analgesics, non-narcotic/therapeutic use, and opioid use*. Additionally, a citation search was performed manually and utilizing Google Scholar to review cited articles of interest.

The following were inclusion criteria: randomized controlled trials (RCTs), practice guidelines, epidemiologic statistics, observational studies, case series, and case reports involving human subjects published in the English language, in peer-reviewed journals in full-text form, or on a professional specialty website addressing the PICO question and studies in which only one dose of Ofirmev 1,000mg was used as an adjunct to standard neuraxial or general anesthesia. The ACOG committee opinion article was utilized to offer a compelling insight into the problem and recommendations from the ACOG and SMFM.

The literature was appraised and classified by level according to the method proposed by Melnyk and Fineout- Overholt. The hierarchy of evidence described in this method ranges from level I (systematic review or meta-analysis of randomized controlled trials) to level VII (expert opinion). Fifty sources were found; after reviewing the sources and removing duplicates, 14 met the inclusion criteria. After consideration of all inclusion and exclusion criteria, six articles remained (Table A1).

Cesarean Birth Trends

According to the US National Center for Health Statistics (2017), cesarean section is the most common operating room procedure in US hospitals, with a national cesarean rate of 32% of all births reported in 2015. The ACOG outlines how pain and fatigue are the most commonly reported problems in the early postpartum period. There is a significant gap in the pain management of the rapidly growing cesarean population in the US and the need for standardization of pain practices to provide adequate pain control in the postpartum period (ACOG, 2018). Despite the standard use of neuraxial anesthesia with opioid adjuncts, research shows an increasing trend in inadequately managed post-cesarean pain and a rising prevalence of

opioid use disorder (OUD), reiterating the need for a multimodal (MMA) approach that provides individual pain control while decreasing the use of opioids (Holland et al., 2020).

The gold standard treatment for immediate post-cesarean pain involves neuraxial local anesthetic combined with an opioid, usually morphine. Carvalho and Butwick (2017) report that neuraxial anesthesia is recommended as the preferred anesthetic modality for cesarean section by the American Society of Anesthesiologists and the American Pain Society and that neuraxial opioids provide high-quality post-cesarean pain control. According to Holland et al., (2020), intrathecal or epidural morphine offers 12 to 36 hours of analgesia and is the standard of care for immediate postoperative pain control, as indicated by national obstetric and anesthesia societies guidelines.

Despite the thought that neuraxial opioids provide up to 36 hours of pain control, post-cesarean pain is still a problem. A meta-analysis of 84 references including cohort studies, practice guidelines, and randomized controlled trials (RCTs) conducted by Holland et al., (2020) concluded that optimal post-cesarean pain control includes a multimodal (MMA) approach combining the use of neuraxial opioids, acetaminophen, and NSAIDs as first-line pain relievers, with PO or IV opioids for breakthrough pain. Additionally, guidelines set by a committee of authors vetted by the Enhanced Recovery After Surgery (ERAS) society describe MMA as a critical component in managing post-cesarean pain as part of an enhanced recovery protocol (Macones et al., 2019). Carvalho and Butwick (2017) add the recommendation of around the clock dosing (ATC) scheduling of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) as a core principle of multimodal cesarean pain management.

A randomized, double-blind, placebo-controlled trial conducted by Baskent University School of Medicine demonstrated that preoperative administration of a single IV dose of

paracetamol offered effective pain control while reducing morphine consumption within the first 24-hour post-cesarean period compared with placebo treatments (Ozmete et al., 2016). The researchers in this study used meticulous search strategies, methods, and design. Pain scores were evaluated in frequent intervals, and additional measures like patient satisfaction and side effects were recorded. They noted no conflict of interests, consented patients, and attained proper IRB approval.

The Bazkent study compared the pain of sixty randomized pregnant women having an American Society of Anesthesiologists (ASA) I and II between 18 and 40 years of age scheduled to undergo elective cesarean surgery under general anesthesia. Half received 1,000 mg IV of paracetamol before induction of anesthesia, while the other half received a placebo. Pain was evaluated at 15th, 30th minutes, and 1st, 2nd, 4th, 6th, 12th, 24th hours, and morphine consumption in the first 24 hours postpartum was also tallied.

The authors concluded that the use of paracetamol prior to general anesthesia not only decreased pain scores but morphine consumption by 36% (Ozmete et al., 2016). These results offer a compelling insight into the positive effects of using paracetamol as an adjunct in an MMA approach to post-cesarean pain management. Still, it is essential to note that this study's participants received general anesthesia instead of the standard neuraxial anesthesia for cesarean section.

A meta-analysis including five randomized, placebo-controlled, double-blind studies conducted by Ng et al., (2019) concluded that preoperative IV paracetamol significantly reduced postoperative pain and opioid consumption in the post-cesarean period. The researchers describe a rigorous inclusion and exclusion process and the use of per-protocol analysis and a random-effects model in their methods and design section. The authors mention study limitations causing

heterogenicity due to the different types of anesthetics used (two neuraxial vs. three general), medication administration timing (some 15 minutes before incision and some immediately after induction), and age (patient population ranged from 18-40 years old). This meta-analysis had results similar to the Bazkent study.

Although the researchers encountered some limitations in this study, the results demonstrate that high-level data support preemptive Ofirmev dosing to decrease pain and opioid consumption post-cesarean. The authors also discuss potential benefits found within the literature, like a blunted hemodynamic response to laryngoscopy and reduced nausea vomiting but imply that these findings require additional studies.

Conversely, Towers et al., (2017) determined that a preemptive dose of Ofirmev 1,000mg did not lower postoperative pain score, morphine usage, or overall length of stay. This prospective double-blinded randomized placebo-controlled trial comprised 105 participants, of which 54 received 1,000mg of acetaminophen and 51 the placebo. Comparably these researchers used stringent inclusion and exclusion criteria, statistical testing to validate their results, proper patient consenting, and IRB approval. Dissimilar to the research conducted by Ozmete et al., (2016) and Ng et al., (2019) this study solely evaluated cesarean patients who received neuraxial anesthesia.

The participants received a standard protocol for spinal anesthesia that consisted of an intrathecal injection of 20 mcg of fentanyl, 0.2 mg of morphine sulfate, and 12 mg of 0.75% bupivacaine; the acetaminophen infusion was started just before the start of and was continued during the placement of the spinal (Towers et al., 2017). Another difference in this study is that the researchers collected pain data using a visual analog scale instead of a numerical scale to evaluate pain for the first 48 hours postoperatively. Despite concluding that a preemptive dose of

Ofirmev did not decrease pain or morphine usage, the authors discuss the need for further studies to evaluate the use of acetaminophen as a postoperative adjunct. They concede that significant data supports its use in this manner (Towers et al., 2017).

Theoretical Framework or Conceptual Model or Evidence Based Practice Model

The conceptual model utilized to guide the development of this project is the John Hopkins Nursing Evidence-based Model. This model uses a three-step process focused on the practice question, evidence, and translation to incorporate the latest evidence-based research findings into practice. The lack of implementation and generalizability of a standardized opioid-sparing approach to treating post-cesarean pain makes this model ideal for this project.

The theoretical framework chosen for this project is Havelock's change theory, comprising of six steps performed cyclically throughout the assessing, planning, implementing, and evaluating the process of an evidence-based intervention. This framework is relevant to this project as it proposes a change in the existing way post-cesarean patients' pain is managed at Hendricks Regional Health, with the intent to decrease pain scores and opioid usage in the first 24 hrs.

Goals, Objectives, and Expected Outcomes

This project aims to evaluate the effectiveness of a preemptive Ofirmev 1,000mg IV on post-cesarean pain scores within the first 24 hours postpartum at Hendricks Regional Health. Pain scores charted by unit nurses were measured using a validated NRS Likert scale (0-10). The expected outcomes were average pain scores lower than 5 out of 10 in the intervention group versus the non-treatment group.

Project Design/Methods

A convenience sample of 50 scheduled cesarean patients from Hendricks Regional Health was retrospectively reviewed. Utilizing Havelock's theoretical framework, the numerical results of NRS scores within the first 24 hours postpartum were compared between 18 patients who received the Ofirmev 1,000mg preoperatively and 32 patients who did not receive the intervention.

Project Site

This project took place at Hendricks Regional Health on the Obstetrics unit, at which 1,330 births occurred in 2018 (About Hendricks, 2019). Hendricks Regional Health is a not-for-profit healthcare organization located in rural Danville, Indiana.

Measurement Instrument(s)

The intervention was evaluated by gathering the pain scores of 50 scheduled post-cesarean patients based on a numerical NRS scale of 0-10, as charted by the obstetric nurses in EPIC over six months. These scores were then averaged and separated into less than five and a score greater than five on the Likert scale.

Data Collection

Data were collected by reviewing patient charts via the EPIC electronic charting system. The primary practical consideration was how patients were deidentified; this was achieved using the patient's initials and the last four digits of their medical record number.

Ethical Considerations/Protection of Human Subjects

Hendricks Regional Health Hospital Internal Review Board (IRB) approval was obtained prior to initiating this DNP Project. There were no major ethical considerations or risks involved in this project's participation as standard pain management options are not altered, only retrospectively reviewed. Participant confidentiality was assured by coding the participants using

personal identification numbers. The list of participants and their identifying numbers have been stored electronically in a password-protected laptop, which can only be accessed by the project coordinator.

Data Analysis and Results

Retrospective NRS pain data were collected over six months and compared between the random intervention and non-intervention groups. After comparing NRS scores between the two groups, the intervention's effectiveness was analyzed by comparing the odds ratio of pain within the first 24 hours postpartum between the two groups. The 24-hour post-cesarean pain scores of 50 patients were collected; of the 50 patients, 18 were in the treatment group while 32 were in the non-treatment group; of the treatment group, two patients' pain results were eliminated due to poor NRS charting.

Appraisal of the data collected demonstrates no relationship between the preemptive use of Ofirmev 1,000mg and lower post-cesarean pain scores within the first 24-hours postpartum with an odds ratio of 1.0 (95% CI 0.21 to 4.65, P=1.0); still, this study did have some limitations. One of the main limitations was a small sample size of only 50 patients. Another limitation was the timing of Ofirmev admistration which ranged anywhere from several hours before cesarean to within and hour of incision. Future studies should focus on a larger sample size and specific timeframe of administration.

Conclusion

The management of post-cesarean pain and the incidence of opioid use and misuse is a rising problem requiring the standardization of an optimal pain regimen. Synthesis of literature regarding current techniques utilized in post-cesarean pain management revealed that MMA regimens are the best approach to addressing post-cesarean pain (Carvalho & Butwick, 2017).

The review of literature demonstrates that a preemptive dose of Ofirmev to manage post-cesarean pain may be potentially effective. Still, due to the layered nature of drug administration used in MMA regimens, data regarding only the utilization of one preemptive dose of Ofirmev in conjunction with standard neuraxial cesarean analgesia is limited. Notably, many articles were excluded from the literature review that utilized multiple doses of Ofirmev throughout the pre and postoperative periods and in combination with other PO or IV drugs on a scheduled basis.

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Ozmete, O., Bali, C., Cok, O. Y., Ergenoglu, P., Ozyilkan, N. B., Akin, S., Kalayci, H., & Aribogan, A. (2016). Preoperative paracetamol improves post-cesarean delivery pain management: a prospective, randomized, double-blind, placebo-controlled trial. *Journal of Clinical Anesthesia*, *33*, 51–57. https://doi.org/10.1016/j.jclinane.2016.02.030

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Appendix A

Table A1

Author/Title/Journal	Purpose	Design/References	Level of Evidence	Result
Holland, E., Sudhof, L. S. & Zera, C. (2020). Optimal pain management for cesarean delivery. International Anesthesiology Clinics, 58(2), 42–49. doi: 10.1097/AIA.0000000000000272.	1. Review options for pain management after cesarean delivery for both opioid-naive women and those with opioid dependence. 2. Review system-wide approaches to help prevent OUD and improve quality of care for women with OUD.	Meta-analysis 84 references	Level I	1. Optimal pain control after cesarean delivery includes a multimodal strategy utilizing intrathecal or epidural opioids, acetaminophen, and nonsteroidal anti-inflammatory agents as a first-line, with oral or parenteral opioids reserved for breakthrough pain. 2. Additional options are relatively understudied and should be individualized to patient needs. Women with stable OUD should continue medication-assisted therapy perioperatively; however, data are limited to guide pain control beyond standard approaches. 3. System-wide strategies should include implementing ERAS protocols and maternal safety bundles to achieve optimal pain management, minimize excess opioid prescribing, and provide standardized multidisciplinary care for women with OUD.
Carvalho B, Butwick AJ. Postcesarean delivery analgesia. Best Pract Res Clin Anaesthesiol. 2017 Mar;31(1):69-79. doi: 10.1016/j.bpa.2017.01.003. Epub 2017 Jan 12. Review. PubMed PMID: 28625307.	Review literature to determine best post-cesarean analgesia delivery	Systematic Review Ref # 93	Level I	1. It is recommended that women undergoing cesarean delivery receive neuraxial morphine (or equivalent long-acting opioid) with"round-the-clock" NSAIDs and acetaminophen for 2 to 3 days following surgery. 2. Systemic opioids should only be prescribed as needed for considerable pain, not responding to opioid-sparing multimodal analgesics, i.e., NSAIDs and acetaminophen. 3. Oral opioids, such as oxycodone, hydrocodone, and tramadol, are recommended to treat moderate to severe breakthrough pain. Intravenous opioids should be reserved only for patients with extreme pain or who are intolerant of oral intake. 4. Alternate clinical care pathways may be required for women with risk factors for severe postoperative pain, such as general anesthesia, extended vertical skin incisions, and a known history of chronic pain.
Ng QX, Loke W, Yeo WS, Chng KYY, Tan CH. A Meta-Analysis of the Utility of Preoperative Intravenous Paracetamol for Post-Caesarean Analgesia. Medicina (Kaunas). 2019 Jul 31;55(8):424. doi: 10.3390/medicina55080424. PMID: 31370298; PMCID: PMC6723542.	Aimed to investigate the utility of preoperative IV paracetamol for post-caesarean analgesia	Meta-analysis	Level I	1. Applying per-protocol analysis and a random-effects model, there was a significant reduction in postoperative opioid consumption and pain score in the group that received preoperative IV paracetamol, compared to placebo.

Ozmete O, Bali C, Cok OY, Ergenoglu P, Ozyilkan NB, Akin S, Kalayci H, Aribogan A. Preoperative paracetamol improves post-cesarean delivery pain management: a prospective, randomized, double-blind, placebo-controlled trial. J Clin Anesth. 2016 Sep;33:51-7. doi: 10.1016/j.jclinane.2016.02.030. Epub 2016 Apr 8. PMID: 27555133.	To evaluate the analgesic effect of preoperative single-dose intravenous paracetamol on postoperative pain and analgesic consumption within 24hours after elective cesarean surgery.	Randomized Controlled Trial	Level I	1. Preoperative use of single-dose intravenous 1g paracetamol was found to be effective in reducing the severity of pain and opioid requirements within 24hours after cesarean section.
Towers CV, Shelton S, van Nes J, Gregory E, Liske E, Smalley A, Mobley E, Faircloth B, Fortner KB. Preoperative cesarean delivery intravenous acetaminophen treatment for postoperative pain control: a randomized double-blinded placebo control trial. Am J Obstet Gynecol. 2018 Mar;218(3):353.e1-353.e4. doi: 10.1016/j.ajog.2017.12.203. Epub 2017 Dec 21. PMID: 29274831.	The primary study objective was to see if maternal opioid use was significantly less in the postoperative period for the study group that received 1 g of intravenous acetaminophen preoperatively compared with a control group that received a placebo. The secondary objectives were to evaluate the maternal length of stay and pain scores postoperatively and assess the acetaminophen level in cord blood at delivery.	Randomized Controlled Trial	Level I	1. the use of a preoperative 1-g intravenous dose of acetaminophen does not decrease the number of opioid medication doses or the morphine milligram equivalents administered postoperatively, nor does it reduce the length of stay postcesarean. 2. The administration of 1-g intravenous acetaminophen preoperatively does not result in elevated newborn cord blood levels.
ACOG Committee Opinion No. 742: Postpartum Pain Management. (2018). Obstetrics and gynecology, 132(1), e35–e43. https://doi.org/10.1097/AOG.0000000000002683	Recommendations for postpartum pain. Stepwise approach. C-section recommendations.	Expert Opinion Ref #64	Level VII	1. Pain and fatigue most significant issues postpartum. 2. Pain interferes with self-care and baby care. 3. Stepwise, MMA emphasizing non-opioid analgesia is safe and effective. 3. Discharge with fewer opioids