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Effectiveness of Intravenous Acetaminophen Administration in the Postoperative Pain Management of the Cesarean Delivery Patient

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Abstract

Intravenous (IV) acetaminophen has been used internationally as part of a multimodal approach to pain management for general surgeries and in some cesarean deliveries for postoperative pain management. In the case of post-cesarean pain management, however, little evidence supports the use of IV acetaminophen. The purpose of this evidenced-based literature review was to determine whether IV acetaminophen reduces opioid requirements for elective cesarean deliveries with neuraxial anesthesia. Google Scholar, CINAHL, PubMed, Cochrane, and Medline were searched. Articles addressing IV acetaminophen and cesarean delivery with neuraxial anesthesia were included. Outcome measurements were specific for postoperative opioid requirements, pain control satisfaction, and visual analogue scores. The literature review resulted in 3 randomized controlled trials with a total of 225 patients, of which 112 received IV acetaminophen. Two studies used fentanyl, and 1 used morphine. All articles found IV acetaminophen improved outcomes; 3 articles suggested that IV acetaminophen in combination with a nonsteroidal anti-inflammatory drug was more effective. Analysis of the evidence revealed IV acetaminophen is a valuable component of multimodal therapy in the reduction of post-cesarean opioid requirements. On the basis of the current body of evidence, we can reasonably recommend IV acetaminophen for elective cesarean delivery patients using neuraxial anesthesia.

INTRODUCTION

Intravenous (IV) acetaminophen has been used internationally to relieve pain in many surgical arenas. With the recent release of IV acetaminophen (Ofirmev; Mallinckrodt Pharmaceuticals) in the United States, many anesthetists have implemented using it for post-cesarean-delivery pain management, despite the lack of evidence supporting its use. An attractive feature supporting the use of IV acetaminophen in multimodal pain management for this population of patients is that it can reduce the overall side effect profile while reducing post-cesarean opioid consumption. Intravenous acetaminophen is typically administered as a onetime dose at the end of the surgical procedure, and research supports its use in various surgical procedures.[1,2] What makes IV acetaminophen so attractive in the cesarean delivery patient who has received regional anesthesia with neuraxial opioids is the limited number of medications available to treat any breakthrough pain. Because of this, many practitioners began administering IV acetaminophen at the end of the cesarean delivery in an effort to reduce breakthrough pain and the need for supplemental opioids beyond those administered neuraxially. While there are many benefits for administration of IV acetaminophen, we should also discuss that a percentage of adult patients may have some adverse effects such as nausea, vomiting, insomnia, and headache. Pediatric patients are susceptible to those adverse effects with a potential for pruritus, constipation, agitation, and atelectasis as well.[3] This article aimed to explore the efficacy of IV acetaminophen use in multimodal therapy to decrease overall opioid requirements in post-cesarean pain management. Our PICOT (population, intervention, comparison, outcome, time frame) research question thus examined the efficacy of IV acetaminophen as an adjunct to spinal anesthesia techniques with local anesthetics (bupivacaine and lidocaine) along with intrathecal opioids (fentanyl and morphine) in minimizing the incidence of rescue opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) for postoperative pain management during the first 24 hours after cesarean delivery. The purpose of this evidenced-based literature review was to determine whether IV acetaminophen reduces opioid requirements in patients who have elective cesarean deliveries with neuraxial anesthesia.

Analysis of the literature suggests that IV acetaminophen is effective in reducing surgical opioid requirements. Arici et al1 conducted a prospective randomized controlled trial to evaluate the effectiveness of IV acetaminophen in patients undergoing total hysterectomy and found that 1 g IV acetaminophen 30 minutes before induction decreased visual analogue scale (VAS) scores, decreased total morphine consumption over 24 hours, produced fewer side effects, and even decreased length of stay in the hospital. This study further purported that 1 g IV acetaminophen is comparable to 10 mg morphine.[1] Remy et al2 conducted a meta-analysis that showed acetaminophen, oral or IV, reduced morphine consumption in surgical patients of amounts up to 10 mg (approximately 20%) in the first 24 hours. It is important to note that this meta-analysis did not restrict its population to obstetric surgery and that acetaminophen was administered both intravenously and orally.[2] The meta-analysis included a study by Siddik et al,[4] which examined a small sample of elective cesarean delivery patients who received neuraxial anesthesia, IV propacetamol (a prodrug form of acetaminophen), and oral diclofenac. In this study, diclofenac compared to propacetamol significantly reduced morphine consumption postoperatively.[4] Newer studies have replicated those results with a positive correlation in treatment with IV acetaminophen in conjunction with diclofenac for a decrease in postoperative opioid consumption.[5] Additionally, Munishankar et al[6] found that patients who received a combination of diclofenac and paracetamol required less morphine than did those given paracetamol alone. One limitation is the route of delivery for the medications; it was given as a suppository.[6] The article failed to address whether diclofenac alone or paracetamol alone showed a significant difference. These studies were included to acknowledge that using a multimodal approach to pain therapy, including IV acetaminophen, is worthwhile. The limitations of this analysis include a small sample size of articles available for the literature search.

The present article focused on the obstetric population undergoing cesarean delivery with spinal anesthesia. The independent variable examined was IV acetaminophen administered after spinal anesthesia using hyperbaric bupivacaine or lidocaine and intrathecal opioids. Control groups included those who received placebo with IV opioids during the perioperative period. Evaluated dependent variables included the incidence of rescue opioids using the different objective scales as outlined in Appendix A. Other studies included were for supportive information regarding pharmacokinetics and pharmacodynamics.

HISTORY

Intravenous acetaminophen recently entered the market in the United States with the brand name Ofirmev.[3] Patients who are unable to take medications by mouth or who may have absorption issues can be given this IV formulation as an adjunct in multimodal therapy in the perioperative period. Many practitioners refrain from using IV ketorolac owing to patient allergies, platelet dysfunction, or renal status. However, IV acetaminophen may be used in place of IV ketorolac.

Opioid administration has a dose-dependent side effect profile that includes nausea, vomiting, and respiratory depression that can delay discharge times.[3] Additionally, the use of IV opioids is often limited in the cesarean delivery population owing to the concomitant administration of intrathecal opioids with a local anesthetic for postoperative analgesia, thereby limiting opioid administration within the first 24 hours following surgery.[7]

Acetaminophen is a centrally acting analgesic and antipyretic; however, the exact mechanism of action is not completely understood.[8,9] Some authors have proposed that acetaminophen inhibits the nitric oxide synthesis pathway and inhibits prostaglandin synthesis.[10] Although other studies agree with the nitric oxide pathways, they also provide information about the possibility of inhibition of cyclooxygenase, opioidergic, N-methyl-D-aspartate receptor (NMDA) inhibition, serotonergic, and endocannabinoid systems as a mechanism of action.[7-12] Acetaminophen dosing and administration considerations include hepatic first-pass metabolism and potential hepatic damage whether the route is oral, rectal, or IV. The bioavailability of medications administered affect timing for prescribing them in a multimodal therapy model. The maximum blood concentration (Cmax) of acetaminophen given intravenously is 29 mcg/mL, that for the oral formulation is 14.2 mcg/mL, and that for the rectal formulation is 10.3 mcg/mL.[13] Pharmacokinetic information indicates that dosing of IV acetaminophen does not reach the hepatotoxic levels of 150 mcg/mL, even with repeat dosing.[14]

Kulo et al[15] collected plasma or urine samples from 39 women scheduled for elective cesarean delivery to evaluate the pharmacokinetics of IV paracetamol. Eight of these women were then enrolled again for evaluation at weeks 10 and 15 postpartum for evaluation of clearance. According to their plasma concentration factors, women show a higher clearance of paracetamol at delivery than at 12 weeks postpartum. The information presented suggests that the likelihood of hepatotoxicity should be decreased. The article does note that because there is a higher clearance to potentially hepatotoxic oxidative metabolites at delivery, one may consider a higher dosing during this period. Additional research is needed to determine the incidence of hepatotoxicity with the current recommended perioperative dose of 1 gram IV acetaminophen in elective cesarean delivery patients.[15] Moreover, hepatotoxicity has not been widely examined as an adverse reaction, even with a onetime dose.

Multimodal therapy is accepted as common practice today owing to its ability to be specific and sensitive to each patient's pain management requirements. However, it should also be noted that the cost of IV acetaminophen has more than doubled in the United States between 2013 and 2014. The usual cost per dose to the hospital at wholesale was $12 to $13 in 2013 and is now more than $35.[3,14] Ordinarily, an increase in the price of the medication would translate to an increase in cost to the patient. Because billing is typically a whole collected fee in the elective cesarean delivery patient population, research studies have not evaluated the cost-effectiveness of IV acetaminophen in this scenario. The cost-effectiveness of IV acetaminophen can also be an eliminating factor to a hospital's choice to carry the drug on formulary and its consistent use within a particular population.

REVIEW OF THE LITERATURE

An extensive literature review was performed by using Google Scholar (Google Inc), CINAHL (EBSCO Health), PubMed (US National Library of Medicine), Cochrane Library (Cochrane), and MEDLINE (US National Library of Medicine) to evaluate the PICOT question. Keywords used in the search were as follows: IV acetaminophen, paracetamol, cesarean section, spinal anesthesia, epidural anesthesia, neuraxial anesthesia, and postoperative pain.

Articles were excluded on the basis of pain medication, method of delivery, and year of available articles. Any article older than 5 years was not included in the analysis, but may have been included in the supportive data. A total of 3 articles met all inclusion criteria. All 3 were prospective randomized controlled studies. Three randomized controlled trials included a total of 225 patients, 112 of whom received IV acetaminophen. All studies utilized neuraxial anesthesia with an adjunct of fentanyl[11,12] and morphine (Duramorph; West-Ward Pharmaceuticals)8 for primary pain management and a prescribed multimodal pain management plan. All evaluated whether IV acetaminophen and neuraxial anesthesia had any impact on decreasing postoperative opioid requirements. Two articles suggested that IV acetaminophen in combination with an NSAID was superior to IV acetaminophen alone.[5,11] Evaluation of the evidence in the articles is noted in Appendix A; a critique of all 3 articles is noted in Appendix B.

Analysis of the evidence revealed that IV acetaminophen is effective in reducing cesarean delivery postoperative opioid requirements.[8,11,12] VAS scores showed a statistically significant reduction ($P<0.05$) in the side effect profile at 4 hours and 24 hours postoperatively.[8,11] The prospective randomized controlled trial by Atashkhoyi et al[12] showed an increased time to first analgesic and decreased time to ambulation with decreased cumulative postoperative analgesic consumption than the study group receiving a placebo. These findings were reinforced in another prospective, double-blind randomized placebo-controlled study by Omar and Issa[8] with findings showing no rescue drug required in the IV acetaminophen group as compared to 25% of the control group who required multiple doses of meperidine for pain control. This can be attributed to adjunct administration of IV acetaminophen and is thought to be directly proportionate to decreased overall opioid requirements.[8,11,12]

Alhashemi et al[11] analyzed a spinal anesthetic technique with 8 to 10 mg of hyperbaric bupivacaine plus 10 mcg fentanyl and the effectiveness of IV acetaminophen compared with those of an oral NSAID as part of the multimodal pain management plan. A morphine IV patient-controlled anesthesia (PCA) device with settings of 2-mg bolus, 10-minute lockout, and no basal infusion was included for opioid requirement measurement.[11] Atashkhoyi et al[12] examined a spinal anesthetic technique with 1.5 mL of hyperbaric lidocaine and 15 mcg fentanyl. Spinal anesthesia was confirmed and then the patients were randomized into 2 groups of patients receiving IV acetaminophen and a placebo, 20 minutes before the end of the procedure. Omar and Issa[8] examined a spinal anesthetic technique with 8 to 10 mg of hyperbaric bupivacaine with 0.2 mg morphine (Duramorph; West-Ward Pharmaceuticals). After a T4 sensory deficit was achieved, patients were randomly divided into 2 equal groups. One group received IV acetaminophen (1 g/100 mL) at the end of the procedure and every 6 hours for 24 hours. The second group received a placebo 100-mL infusion at the same time intervals.[8] Breakthrough pain, antiemetic therapy, and opioid consumption were measured throughout the perioperative period. A VAS for pain measurement ranging from 0 to 10 was utilized throughout the studies. Time to first analgesic rescue, ambulation time, antiemetic therapy, and hemodynamic changes were analyzed for the first 24 hours postoperatively.

DISCUSSION

Although the studies followed a prospective design, some problems were noted in each. For example, in the study by Alhashemi et al,[11] a post hoc analysis showed 160 patients were needed to demonstrate a statistical difference and a follow-up study was not done. No statistical data were available at 48 hours postoperatively.[11] In addition, the differing routes of medication administration between IV acetaminophen and oral ibuprofen could have confounded the outcomes. In terms of the second study by Atashkhoyi et al,[12] this research was published in a journal without the benefit of peer review and the authors did not elaborate on the study's limitations. Despite these limitations, the design was sound in that it was a randomized controlled trial and the findings were relevant, hence the reason this study was chosen for review. In the final study included for critical review by Omar and Issa,[8] it was noted that the study used a convenience sample of 80 subjects, which may pose a threat to external validity. However, the use of a convenience sample is common in obstetric anesthesia protocols and all of the studies were done within standards of practice for clinical research and used appropriate statistical analysis.

SUMMARY

Postoperative pain after cesarean delivery can be severe for some women and even debilitating for others. Such pain prevents these mothers from being able to care for their newborn effectively. Intravenous patient-controlled analgesia can be associated with incorrect programming, anxiety about self-administering narcotics, patient ignorance, and sedation with or without respiratory depression.[7] As a result, neuraxial anesthesia methods using spinal applications, with the addition of opioids, and patient-controlled epidural analgesia are being chosen more often as the primary method for pain control within the first 24 hours after delivery. These methods of pain control help prevent drowsiness and enable the mother to care for her baby. Research that evaluates the effectiveness of IV acetaminophen in the obstetric population is limited. In this article, we assessed only those studies that looked at the effect of IV acetaminophen in comparison with other conventional analgesics administered at the time of cesarean delivery. Although the literature was limited, we did show that IV acetaminophen was efficacious in reducing overall analgesic requirements and increasing postoperative maternal satisfaction without the adverse events associated with opioids or NSAIDS. A decrease in overall opioid requirements and an increase in patient satisfaction scores were achieved with IV acetaminophen.

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APPENDIX A: EVIDENCE TABLE FOR RESEARCH STUDIES						
Author, year	Study Objective/ Interventions or Exposures Compared	Design	Sample (N)	Outcomes Studied (How Measured)	Results	Quality[a]
Alhashemi et al (2006)	To compare IV acetaminophen with oral ibuprofen in combination with morphine PCIA after cesarean delivery with spinal anesthesia using hyperbaric bupivacaine and fentanyl	Randomized controlled trial	N=45 women ≥ 37 weeks' gestation scheduled for elective cesarean delivery under spinal anesthesia, randomized to receive IV acetaminophen Q6h plus oral placebo or ibuprofen 400 mg Q6h plus oral placebo. 1st dose given orally 30 min preoperatively All patients received morphine PCIA for 48 h	Intraoperative newborn's Apgar scores recorded at 1 and 5 min Postoperatively pain scores assessed Q1h X 4 h, then Q4h X48 h using the VAS [0 (no pain) to 10 (worst pain)] at rest, documenting morphine requirements along with PCIA attempts made and patient level of sedation Postoperative adverse events such as nausea, vomiting, pruritus, respiratory depression, and oxygen desaturation Patient satisfaction recorded [1 (extremely dissatisfied) to 10 (extremely satisfied)] 48 h postoperatively	VAS scores decreased similarly in both groups over time Statistical decrease in the opioid requirement in both the IV acetaminophen and oral ibuprofen intervention groups (=0.001) IV acetaminophen is a reasonable alternative as an adjunct to morphine PCIA after cesarean delivery for patients unable to receive NSAIDS	IA
Atashkhoyi et al (2014)	To evaluate the analgesic effect of preventive (20 min prior to surgery finish) 1 g IV paracetamol on postoperative pain and analgesic consumption during the 24 h after elective cesarean delivery using hyperbaric lidocaine with fentanyl	Prospective, randomized, and double-blind clinical trial	100 pregnant women, ASA I-II, aged 18-39 years, and term pregnancy undergoing elective cesarean delivery with spinal anesthesia Patients preloaded with 10-12 mL/kg of Lactated Ringer's solution After delivery patients randomly block-assigned to receive one of the 2 study solutions: 1 g IV paracetamol in 100 mL normal saline over 15 min and placebo group with normal saline alone, 20 min prior to the end of the procedure.	Time to first analgesic rescue, time of ambulation, and side effects (nausea, vomiting, sedation, and hemodynamic changes) were measured using a VAS [0 (no pain) to 10 (worst pain)] in the PACU and during the first 24 h postoperatively	Increased time to first analgesic in the study group in the PACU (P<0.0001) and decreased time to ambulation (~5 h) than those in the placebo group (P<0.001) Cumulative postoperative analgesic consumption was lower in the study group (P<0.001) Preventive administration of 1 g IV paracetamol reduces the intensity of pain in the PACU and until 4 h after operation and analgesic consumption following cesarean delivery Incidence of adverse effects did not differ significantly between 2 groups	IA
Omar & Issa (2011)	To evaluate the analgesic efficacy of IV paracetamol (Perfalgan) for pain control after cesarean delivery using hyperbaric bupivacaine with 0.2 mg of intrathecal morphine	Prospective, double-blind, randomized, placebo-controlled study Experimental study-comparative effectiveness Ordinal measurement	Patients were randomly divided into 2 equal groups by a table of randomization 80 ASA I-II women who had elective cesarean deliveries under spinal anesthesia with spinal morphine	VAS was used to evaluate pain level (0 = no pain to 10 = worst pain) at 6, 12, and 24 hours postoperatively by a resident and nurse who did not know about the treatment protocols Satisfaction was evaluated at 12 and 24 hours postoperatively (1 = very unsatisfied to 5 = very satisfied). SPSS version 15 was used to analyze the data. Student's t-test, chi-square test, and Mann-Whitney U-test were used where appropriate for statistical analysis. P-value of < 0.05 was considered statistically significant	In the IV paracetamol (group I), no patients required rescue drug compared to 25% in the meperidine (group II) rescue medication group who required multiple doses to control pain (<0.05) Median pain scores were less in group I at 6 hours [1 (range 1-6) vs. 3 (range 1-8), P = 0.002] at 12 hours [2 (range 0-5) vs. 3 (range 0-7), P = 0.031], and at 24 hours [1.5 (range 0-4) vs. 3 (range 1-8), P< 0.0001], respectively Satisfaction was comparable in both groups IV paracetamol is an effective treatment option and can be used to reduce the requirement of rescue opioid drugs for pain control after cesarean delivery	IA

Abbreviations: ASA, American Society of Anesthesiologists; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PACU, post-anesthesia care unit; PCIA, patient-controlled intravenous analgesia; VAS, visual analogue scale.
[a]Rating quality of study (Newhouse et al., 2007).
Level:
I: Evidence from experimental study, RCT, or meta-analysis of RCTs.
II: Evidence from quasi-experimental study.
III: Evidence obtained from a nonexperimental study, qualitative study, or meta-synthesis.
Quality Rating Scheme:
A: High – consistent results with sufficient sample, adequate control, and definitive conclusions; consistent recommendations based on extensive literature review that includes thoughtful reference to scientific literature.
B: Good – reasonably consistent results; sufficient sample, some control, with fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence.
C: Low/major flaw – Little evidence with inconsistent results; insufficient sample size; conclusions cannot be drawn.

APPENDIX B: CRITIQUE TABLE			
Author, year	Study Objective/Intervention or Exposures Compared	Strengths	Weaknesses
Alhashemi et al (2006)	To compare IV acetaminophen with oral ibuprofen in combination with morphine PCIA after cesarean delivery with spinal anesthesia using hyperbaric bupivacaine and fentanyl	-Experimental study design with randomized controlled trial -Institutional ethics committee approval/written informed consent obtained -Clearly defined inclusion and exclusion criteria -Groups were nearly equal size (N=22; N=23) -Measurement scale was specific and sensitive -Two-sided alpha=0.05 -Power analysis of 90% showing appropriate sample size, low chance of Type II error -ANOVA used at the allotted time course to analyze the effects of therapy -Fisher's exact test for postoperative analysis -Number of PCIA attempts analyzed with Mann-Whitney U-test (ordinal measurement) -Statistical procedures completed using SPSS software -Evaluating alternative but equal therapy for multimodal analgesia. No statistical differences noted for either adjunct therapy within 48 h postoperative time frame -Results, Discussion, and Limitations identified weaknesses of the study	-Post hoc power analysis showed 160 patients necessary to demonstrate statistical difference -Follow-up study not done -Different route of administration (IV acetaminophen vs. oral ibuprofen) could account for lack of variance -Limited applicability of study to patients undergoing cesarean delivery with spinal anesthesia with Duramorph -No dose-response curves available for studied medications
Atashkhoyi et al (2014)	To evaluate the analgesic effect of preventive (20 min prior to surgery finish) 1 g IV paracetamol on postoperative pain and analgesic consumption during the 24 hours after elective cesarean delivery using hyperbaric lidocaine with fentanyl	-Experimental study design with double-blind randomized controlled trial -Institutional ethics committee approval/written informed consent obtained -Clearly defined inclusion and exclusion criteria -Groups were equal size (N=50; N=50) -Measurement scale was specific and sensitive -Two-tailed alpha=0.05 -Power analysis of 80% showing appropriate sample size, low chance of Type II error -Compared the efficacy of preventive administration of paracetamol with patients who received placebo to eliminate variables -Provided a thorough statistical analysis in an effort to prevent a Type II error by analyzing the means using Student's t-test, medians using Mann-Whitney U-test, counts using Fisher's exact and X2 tests -Statistical procedures completed using SPSS software	-Limitations of study not well discussed -No dose-response curves available for studied medications -Patients were not followed up with regards to chronic pain management - Studies did not have preoperative analgesic injection (preemptive) group as an example of the importance of timing the dosage of IV paracetamol
Omar & Issa (2011)	To evaluate the analgesic efficacy of IV paracetamol (Perfalgan) for pain control after cesarean delivery using hyperbaric bupivacaine with 0.2 mg of intrathecal morphine	-Experimental study design with double- blinded randomized controlled trial -Approval from institutional ethics committee/ written informed consent from patients -Appropriate inclusion and exclusion criteria -Randomization table for data assessed using X2 test, Mann-Whitney U-test, and Fisher's Exact test where appropriate ($P < 0.05$ is significant) - Results showed no statistical significance for patient demographics, but statistical significance for amount of rescue medications needed -Limitations of the study clearly stated	-Small sample size -Results limited to comparison of IV paracetamol, placebo group and rescue medication -Non-probability convenience sampling may pose a threat to external validity

Abbreviations: IV, intravenous; PCIA, patient-controlled intravenous analgesia.