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Research Article

The Analgesic Efficacy of IV Acetaminophen for Acute Post-Operative Pain in C-Section Patients: A Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

Objective: Our study sought to isolate and assess whether IV acetaminophen in four divided doses over 24 hours decreased pain scores and opioid requirements in patients undergoing cesarean delivery with neuraxial anesthesia.

Methods: The primary objective of this study was to evaluate the effectiveness of IV acetaminophen in reducing 24-hour opioid requirements. A total of 66 patients undergoing elective cesarean delivery under spinal anesthesia with hyperbaric bupivacaine 12 mg, fentanyl 10 µg, and preservative-free morphine 150 µg were randomized to receive either IV acetaminophen or IV placebo for four consecutive doses in the first 24 hours post-operatively. The need for rescue medication using morphine equivalence, pain scores, patient satisfaction, and side effects was assessed by a blinded researcher in the first 24 and 48 hours post-operatively.

Results: 165 subjects were approached for the study, 84 subjects agreed but 18 did not fulfill the inclusion criteria. Ultimately, 66 were enrolled. There was no difference in opioid requirements in the acetaminophen vs. placebo group, 44.32 ± 23 mg vs. 47.59 ± 28 mg (p=0.607) morphine equivalence, respectively at 24 hours. There was also no difference at 48 hours, 57.95 ± 20 mg vs. 56.59 ± 22mg morphine equivalence (p= 0.795). Post-operative pain scores, patient satisfaction, and adverse events were similar in both groups as well.

Conclusion: The results of this study failed to demonstrate any additional benefits of administering multiple doses of IV acetaminophen for treating post-operative pain in patients who have undergone CS surgery and receiving intra-thecal morphine as part of their anesthesia and analgesia.

ABBREVIATIONS

IV: Intravenous; CD: Cesarean Deliveries; OSA: Obstructive Sleep Apnea; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; IRB: Institutional Review Board; CONSORT: Consolidated Standards of Reporting Trials; ASA: American Society of Anesthesiologists; PS: Physical Status; NRS: Numerical Rating Scale; PCA: Patient-Controlled Analgesia

INTRODUCTION

The number of elective cesarean deliveries (CD) in the United States is increasing each year, and currently, the rate in the US is about 33% [1]. Post-operative pain control for CD is more complicated than for elective abdominal surgery. In addition to typical pain arising from the surgical wound, the CD is complicated by pain from contraction of the uterus. Earlier studies have demonstrated that inadequate pain control after CD is related to adverse childbirth experience, increased risk of postpartum depression, and poor maternal-infant bonding [2]. Given the complexity of the pain pathways after CD, a multimodal approach might be beneficial for the pain management of these patients. Although there have been substantial improvements in analgesia strategies, the optimal drug for post-operative pain management remains a clinical dilemma. Obesity, obstructive sleep apnea (OSA), and the rise in opioid dependence further complicate the pain management [3]. While opioids alone and in combination with non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medication after CD, opioid-related side effects and the danger of using NSAIDs, such as bleeding, ulcers, and platelet inhibition, warrants the search for a safer alternative.

The use of IV acetaminophen as part of a multimodal analgesic regimen has proven clinically effective and cost-effective in treating post-operative pain. Several studies conducted in CD patients and other surgical subspecialties have demonstrated the efficacy of IV acetaminophen in reducing post-operative opioid consumption, opioid-related adverse events, post-operative

nausea and vomiting, improvement in post-operative sedation level, and patient satisfaction [4-9]. We use intrathecal morphine as the standard of care at our institution and wanted to determine if the addition of IV acetaminophen would further decrease narcotic supplementation. In a recently published double-blinded randomized controlled study the use of IV acetaminophen in the post-operative period after CD has resulted in a significant reduction in opioid consumption [9]. None of the studies have used IV acetaminophen as a standalone option for post-operative pain management. Recognizing the need for a safer alternative to treat post-operative pain in CD patients, we hypothesized that administration of IV acetaminophen in the post-operative period would reduce opioid requirements. We performed a randomized, double-blind placebo-controlled study with goals (1) to evaluate the effectiveness of 4 doses of IV Acetaminophen in reducing 24-hour opioid requirements in CD patients and (2) to assess the efficacy of 4 doses of IV acetaminophen in reducing numerical rating scale (NRS) pain scores.

MATERIALS AND METHODS

We performed a randomized, double-blind placebo-controlled study in line with guidelines of the Helsinki Declaration. This study was approved by the Albert Einstein College of Medicine Montefiore Medical Center Institutional Review Board (IRB). Even though IV acetaminophen was not approved for the use in pregnant woman considering the first dose of administration of the study drug was after the cord clamp, the study population was not deemed as pregnant, and the study was approved as a minimal risk study. We registered the study prospectively on clinicaltrials.gov NCT02069184. This manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The only change we made after the commencement of the study was to increase the sample size by 10%; this was to accommodate for spinal failures. There were no other changes to the methods or trial outcomes after the trial commenced, and we performed no interim analysis

Eligible participants were patients scheduled for elective full-term CD, were ≥ 18 years of age, and had an American Society of Anesthesiologists (ASA) Physical Status (PS) score II-III.

Exclusion criteria encompassed allergic reaction to IV acetaminophen, pregnancy-induced hypertension or pre-eclampsia, planned intensive care admission, severe hepatic impairment or active liver diseases (two-fold increase in any of the pre-operative liver enzymes), pre-operative serum creatinine >2mg/dl, any evidence of hepatic dysfunction of the newborn in nursing mothers, an inability to use neuraxial anesthesia, chronic opioid usage, or if the CD was emergent.

Perioperative anesthesia management

Before CD, all subjects enrolled in the study received the standard of care medications, and all standard monitors were applied. The spinal anesthesia technique was standardized. Hyperbaric bupivacaine 12 mg, fentanyl 10 μg, and preservative-free morphine 150 μg were used for administering spinal anesthesia. A 25 gauge Whitacre needle was used to administer spinal anesthesia. A T4 surgical level was obtained in all cases.

Surgery proceeded via a Pfannenstiel incision. We did not administer any prophylactic antiemetics to the patients. Management of Intraoperative discomforts were left to the discretion of the attending anesthesiologist. The uterus was exteriorized in some of the cases. The surgical technique was at the discretion of the obstetrician.

Study drug dosage and administration

In this study, we assigned patients either to receive IV acetaminophen or a lookalike IV placebo. For all patients, 100 ml of the assigned study drug was infusedover a period of 15 minutes. The drug was infused through an intravenous line that was on the subject as part of the routine standard of care. The first dose was given upon cord clamping in the operation room and certain circumstances it was given immediately after the delivery. The second, third, and fourth doses were all administered 6 hours after the first dose.

Breakthrough pain intra-op was treated at the discretion of the anesthesiologist. No nonsteroidal anti-inflammatory drugs (NSAID) were administered intra-op.

Post-operative pain management

Post-operative pain was managed with oral oxycodone every 4 hours pro re nata (PRN). In the first 24 hours, the breakthrough pain was treated with bolus IV morphine, and no NSAIDs and acetaminophen-containing products were used in the first 24 hours.

Outcome assessments

The primary outcome of the study of opioid usage in the 24 hours was collected by reviewing the medical records. Additionally, we also confirmed the medication intake during the periodic assessments. We also collected the opioid usage for 48 hours and during the entire hospital stay. All the opioid medications received by the subjects were converted to morphine equivalence. We used a conservative1: 2 oxycodone: morphine sulfate conversion ratio.

Secondary endpoints such as pain scores were evaluated every 6 hours for the first 24 hours, and every 8 hours for the next 24 hours, using the Numerical rating scale (NRS). The subjects were asked to assess the pain on a scale of 0 to 10, where 0 represented no pain and 10 represented the worst pain imaginable. No pain assessment was conducted on sleeping patients from 10 pm to 6 am. During the nighttime hours, pain scores were collected from the nursing chart. A 30 minute window period was considered when recording pain scores from the nursing charts. We did not assess for a difference in pain at rest versus with movement.

We also collected other endpoints of the study which included the incidence of adverse events, sedation level, time to first bowel movement, length of hospital stay and overall anesthesia satisfaction (pain management) in the two groups. Adverse events were defined as post-operative nausea and vomiting, pruritus and breathing difficulties. Sedation was assessed as a way to validate pain score readings. As sedation was a minimally important outcome, no validated sedation scales were used for the assessment. Sedation was assessed on a scale of 1-3 (1= wide awake, 2= sleepy but easily aroused, 3= sleepy and difficult to arouse). These assessments were made at the same time points as the pain assessments by the same research assistant.

We also surveyed to evaluate patient satisfaction with overall pain management. Patients were given a survey questionnaire at 24 hours and 48 hours post-operatively. Subjects were explicitly asked about their overall pain management satisfaction level. Satisfaction level was assessed on a scale of 0 to 10, with 0 being extremely dissatisfied and 10 being extremely satisfied. Also in the questionnaire, subjects were specifically asked about adverse events like nausea, vomiting, pruritus and breathing difficulties and information regarding their bowel movements. This information was collected on a scale of none, mild, moderate or severe.

Additionally, the mother and the infant were also closely monitored for any adverse events during the hospital stay. After the discharge from the hospital, a research assistant conducted a telephone interview on the seventh day to ensure the wellbeing of the mother and the newborn. All the outcome assessments were collected by a research assistant who was blinded to the treatment group

Randomization

We used randomization.com to create randomization sequences. Subjects were allocated to two groups in the ratio of 1:1. On the day of the surgery, the investigational research pharmacy that is not part of patient care or data collection assigned subjects into one of the two groups. The anesthesiologist or the floor nurse taking care of the patient administered the 100 mL of study medication or 100 mL of normal saline to the patient as assigned.

Statistical analysis

5.6.1. Sample size calculation: The primary objective of this study was to evaluate the effectiveness of IV acetaminophen in reducing 24-hour opioid requirements. The study was powered to be able to show a minimum clinically significant reduction of 20% in opioid usage when compared between the two groups. We calculated that 26 patients in each group would have 81% power to detect a difference of 9mg morphine equivalence. The null hypothesis of the study is 45 ± 11.2 mg morphine equivalence is the number of opioids used by both groups in the first 24 hours, and the alternative hypothesis is less than or equal to 36 ± 11.2 mg morphine equivalence will be used by the intervention group. We calculated our sample size using a t-test for two independent samples with common variance and 0.05 as the significance level. We anticipated that 10% of the data might be incomplete. To accommodate this missing data we increased our sample size by 10%, to a total of 60 subjects in the two groups. Additionally, as mentioned earlier to accommodate for spinal failures, we have increased our sample size to 33 patients per group.

All the analyses were performed with an intention-to-treat approach. The analysis plan assumed that the primary outcome of the trial, the dosage of opioid used (morphine equivalence) was a continuous variable. The total morphine equivalence at 24 hours and 48 hours were analyzed using the student's t-test and was reported as the mean ± standard deviation (95% confidence interval of the mean). We considered pain score as a continuous variable. Each patient had a total of eight pain score recordings. We used mixed-effect model repeated measures to analyze the difference in mean pain scores. The mixed-effect model assumed that repeated measurements in the same individual are not independent and allows individuals to have unequal observations. Treatment, time and interaction treatment X time were set as fixed effects. For this analysis, we used the data sheet with no missing pain scores (data extracted from nursing charts). Categorical variables such as episodes of adverse events were analyzed using the chi-square analysis or Fisher's exact tests. Sedation level and amounts of rescue medication used were analyzed using Mann-Whitney- U test. The nature of the hypothesis testing was 2-tailed, and $P < .05$ was considered statistically significant. All p values reported are unadjusted. Statistical analyses were conducted using SPSS 22 (SPSS, Chicago, IL)

RESULTS

One hundred and sixty-five subjects were approached for the study and out of those, 84 subjects agreed to participate. 18 subjects did not fulfill the inclusion criteria. Ultimately, 66 subjects were randomly assigned to either receive IV acetaminophen or placebo (Figure 1).

There were no significant differences between the groups regarding demographic or surgical data (Table 1). None of the subjects enrolled were on acute or chronic pain medication. All the subjects enrolled were admitted on the same day as their elective surgery. The post CD characteristics (estimated blood loss, post CD hemoglobin) and neonatal outcomes (1 and 5 minute Apgar scores were similar in both groups (Table 2).

Eight patients in total were withdrawn from the study, six from the IV acetaminophen group and two from the placebo group. Regarding withdrawal from the study arm: three patients were withdrawn after receiving the first dose. One was withdrawn for bleeding requiring re-operation. The other two were withdrawn for an unclear reason. Two patients were withdrawn before study drug administration secondary to inadequate intra-op anesthesia and need for supplementation with IV narcotics. The last subject was withdrawn for requesting the NSAID ketorolac. In the placebo group, two patients were withdrawn. One for the accidental administration of two tablets of oral Percocet, as this was a protocol deviation, and the other for request of ketorolac.

The primary outcome of the study the opioid consumption in the first 24 hours did not demonstrate any statistically significant difference between the two groups. The subjects in the IV acetaminophen group received less oral morphine equivalence opioid dosage in the first 24, but the difference was not statistically significant with 44.32 mg (95% CI −36.06-52.58) in the IV acetaminophen group and 47.59 mg (95% CI-37.71- 57.40) in the placebo group. However, in the 48 hour period, subjects in the IV acetaminophen group received more opioids compared to the patients in the placebo group, with 57.95 mg (95% CI- 50.75 -66.15) of opioids in the IV acetaminophen group and 56.59mg (95% CI-48.75-64.43) in the placebo group p-value-0.79 (Table 3).

In the analysis with the missing pain scores, the median (25th -75th percentile) pain scores at thirty minutes, six hours, twelve hours, eighteen hours and twenty-four hours, thirty-two hours, forty hours, and forty-eight hours for each study arm are reported in table 4. The mixed model repeated measures analysis

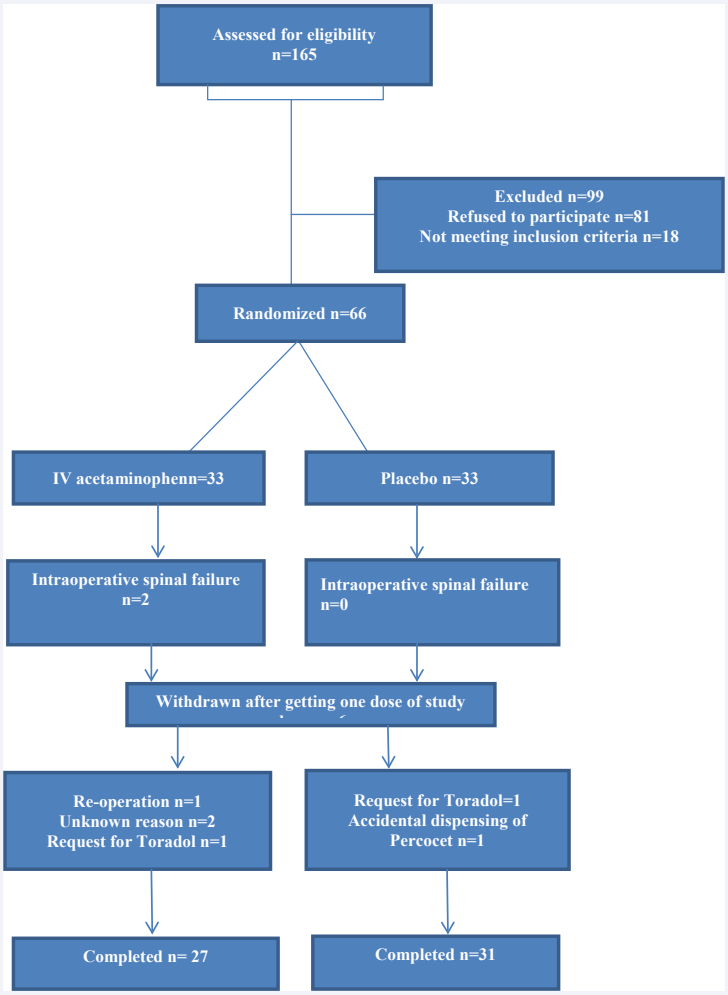

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram depicting subject enrollment and randomization.

Table 1: Values are mean± standard deviation (95% confidence interval of the mean).

	IV acetaminophen (33)	Placebo (33)	P value
Age (years)	31±6 (29-34)	31±5 (30-33)	0.870
BMI (kg/m^2)	33±6(30-35)	36±6(34-38)	0.059
Gravida (pregnancies)	3±1(3-4)	3±2(2-4)	0.610
Para (deliveries)	1±1(1-2)	1±1 (1-2)	0.730
ASA	2(2-2)	2(2-2)	0.781
Pre CS Hb	12±1.4(11-12)	11±1.2(10-12)	0.940
Status CS (Repeat)	76% (25)	73%(23)	0.530

Abbreviations: BMI: Body Mass Index; ASA: American Society of Anesthesiologist; CS: Cesarean Section; HB: Hemoglobin

Table 2: Post CS patient characteristics
Values are mean ± standard deviation (95% confidence interval of the mean)

	IV acetaminophen	placebo	P value
Apgar (5 mins)	9±0.4 (9-9)	9±0.2 (9-9)	0.910
Weight of new born (grams)	3372±615(3146-3598)	3417±552(3218-3616)	0.736
Estimated blood loss (ml)	875 ±161(816-934)	860±122 (816-905)	0.681
Post CS Hb	10 ±1(9-10)	10 ±1(9-11)	0.171

Abbreviations: CS: Cesarean Section; Hb: Hemoglobin

Table 3: 24 hours and 48 hours post-operative total oral morphine equivalence
Values are presented as the mean ± standard deviation (95% confidence interval of the mean), unadjusted p-value

Totaloral morphine equivalence	IV acetaminophen	Placebo	P value
24 hours cumulative	44.32±23 (41.55-47.08)	47.59 ±28 (44.28- 50.90)	0.607
48 hours cumulative	57.95±20 (55.54 -60.37)	56.59±22 (53.96-59.22)	0.795

Table 4: 24 hours and 48 hours VAS Pain Scores Values are presented as median (25th and 75th percentile), unadjusted p-value.

Pain scores	IV acetaminophen	Placebo	P value
30 minutes after CS	1 (0.0-4.0)	0.0 (0.0-3.0)	0.356
6 hours after CS	3.50 (0.0-6.0)	4.0 (2.0-5.0)	0.850
12 hours after CS	0.0(0.0-3.0)	2.0 (0.0-4.0)	0.147
18 hours after CS	3.0 (0.0-4.75)	3.0 (0.0-5.0)	0.663
24 hours after CS	3.0(1.0-6.0)	5.00 (4.0-6.75)	0.066
32hours after CS	3.0 (2.0-5.0)	3.0 (0.0-5.0)	0.871
40 hours after CS	1.0 (0.0- 4.0)	0.0 (0.0-3.50)	0.185
48 hours after CS	3.0 (1.50-5.0)	3.0 (0.0-4.0)	0.542

Abbreviations: CS: Cesarean Section

of VAS pain scores established time effect was significant ($p < 0.001$), but the time versus group interaction was not significant ($p=0.749$). This means that the hypothesis that for both groups the VAS pain scores at all eight-time points are equal was rejected. However, with group interaction hypothesis was evaluated, that the deviations from equality over the eight-time points are same for the two groups was not rejected. The interpretation of this means that "the study group" (IV acetaminophen) did not have any influence on the pain score over the period.

Adverse events reported were minor and were equally distributed among the groups. Nausea, vomiting, itching, and sedation were the adverse events reported. No serious adverse events were reported in either group.

There were no significant differences in sedation between the two groups. 97% of subjects in both groups were reported to be wide awake. None of the subjects in either group reported being sleepy or difficult to arouse. Regarding bowel movement, the majority of the subjectsreported their first bowel movement within the first two days after surgery, 81% in the placebo group versus 67% in the IV acetaminophen group, p 0.34. Overall pain management satisfaction was not statistically different between the groups at 24 or 48 hours. At 24 hours, mean ± SD satisfaction score was 8.3 ± 2.8 vs. 8.2 ± 1.9 in the acetaminophen vs. placebo group, respectively. Satisfaction scores were similar at 48 hours.

The pediatrician evaluated the newborns on post-operative day 2. There was no difference in the health of the newborn in either group. A one-week follow-up phone interview conducted with mother/ family confirmed the wellbeing of the mother and the infant.

There was no change in opioid usage in the 48 hours and no clinically significant advantage regarding the occurrence of adverse outcomes. The decrease in the opioid consumption in the first 24 hours is minimal, and the clinical significance of the "improvement" is questionable.

DISCUSSION

In a recently published randomized controlled study, the use of multiple doses of IV acetaminophen in CD patients has demonstrated a reduction of total opioid consumption during the hospital stay [9]. In this study, they administered six doses of IV acetaminophen in 48 hours. In addition to that post-operative pain management included NSAIDs and oxycodone tablets. Even though the study showed a statistically significant reduction in the total narcotic usage the number of NSAIDs used and the total number of breakthrough pain medications used were not significantly different. The main difference between our study and other published studies is that in our study, no other pain medications were used in the first 24 hours other than oxycodone tablets. To keep the study as pure as possible without the effects of non-steroidal anti-inflammatory drugs (NSAID) being the etiology of the pain relief or the potential synergism between IV Tylenol and the NSAID accounting for the pain relief, we used IV acetaminophen as a standalone drug for the management of post-operative pain. One of the studies from outside the United States had a similar study design as ours. Omar et al., compared IV paracetamol (Perfalgan) to placebo in subjects undergoing CS [10]. Similar to our study, the subjects were given four consecutive doses of IV acetaminophen every 6 hours for 24 hours. Intraoperative spinal anesthesia was achieved by administering bupivacaine and morphine. Meperidine was given to both groups as part of rescue medication for pain. The results of this study were contrary to what we have found in our study. The researchers reported that the subjects in the placebo group required more rescue medication when compared to IV acetaminophen group 25% versus 0% respectively. In our study, no subjects from either group requested additional intravenous rescue medications. Both groups of patients required large doses of morphine equivalent (>44mg on average) because at our institution, the standard of care is between 0.1 mg – 0.2 mg and in our population of BMI that is >35, they require more narcotics. The pain scores reported in their study were significantly lower

in the acetaminophen group at all times. The authors concluded that IV paracetamol was an effective option for post-cesarean section analgesia and can be used to reduce opioid consumption. Total opioid amounts used and any adverse events were not mentioned in the Omar et al., study. We could not reproduce these results. Pain scores in our study followed a fluctuating pattern where both groups had lower and higher pain scores at various intervals.

Similar studies conducted by Kilicaslan have demonstrated significant benefits of using IV acetaminophen in the post-operative period, yet the study conducted by Alhashemi et al., showed no significant difference between the study arms [11,12]. Alhashemi et al., compared IV acetaminophen to oral NSAIDs for post-op analgesia. Forty-five subjects undergoing elective cesarean section received 1 gram IV acetaminophen plus oral placebo every six hours or ibuprofen 400 mg poplus IV placebo. The first dose was given 30 minutes preoperatively and after that every 6 hours for 48 hours. Spinal anesthesia was achieved with 0.5% hyperbaric bupivacaine mixed with 10µg of fentanyl. Post-operative pain was assessed using VAS pain scores (0-10 scale) every hour for the first four hours and then every 4th hour until the 48-hour post-operative mark. The amount of morphine required was collected from morphine PCA pumps, and adverse events were recorded. They found no clinically significant difference in morphine requirements or pain scores between the two groups, albeit they compared IV acetaminophen to another active medication. This study differed from ours in that only a short-acting opioid (fentanyl) was administered via spinal whereas we used both fentanyl and morphine. Despite these differences, they also concluded that IV acetaminophen showed no additional benefit in treating post CD pain.

The incidence of adverse events in our study is comparable to other reported studies. Additionally, it is consistent with the fact that the use of IV acetaminophen in the post-operative period is not associated with a decrease in opioid-induced side effects [13].

A likely explanation for the lack of benefit of IV acetaminophen is the use of intrathecal morphine in our study. Earlier studies have demonstrated that the use of intrathecal morphine reduces pain intensity at various intervals up to 24 hours post-operatively [14]. Even though the exact mechanism of action of IV acetaminophen and its interactions with opioids is still not precise, IV acetaminophen appears to work either directly or indirectly on opioid-containing pathways [15,16]. Perhaps this is the reason that there does not seem to be an added benefit of IV acetaminophen when long-acting intrathecal morphine is utilized.

STUDY LIMITATIONS

There are several limitations to this clinical trial. First, the rescue pain medications were not dispensed in a standardized manner. Although instructions were given on when to administer rescue medications, adherence to the instructions by the clinical personnel could not be verified. The use of patient-controlled analgesia (PCA) pumps could have been utilized to standardize rescue medications, but we standard do not give PCA pumps to patients who receive spinal morphine PF. Post-operative pain management using PCA would have allowed us the collection of the proportion of subjects that required additional rescue medications.

The randomized controlled design of this study is appropriate for controlling of known confounders, considering the smaller sample-size; there can be unknown factors that could have biased the results of the study. For example, genetic predisposition and other psychological factors associated with pain are not accounted for in the analysis. Additionally, mother's negative expectations, anxiety, sensitivity, fear responses, and the birth partner's fear responses are critical psychological factors associated with pain experience after cesarean section [15]. In our study, we did not evaluate any of the above-described factors. Although the percentage of primary and repeat cesarean sections were similar between the two groups in our study, it is entirely possible that the individual subjects in each of the two groups differ significantly in their pain perception. Finally, the study did not account for the variation in potential surgical technique by different surgeons and possibility of post-operative pain management decisions at an individual level.

CONCLUSION

In our single center, double-blinded, randomized placebo-controlled study; multiple doses of IV acetaminophen did not show a benefit in reducing post-op pain scores or opioid requirements when used in conjunction with long-acting neuraxial opioids. Results of this study do not support the introduction of IV acetaminophen for post-operative management after CD. Because long-acting opioids are only used in 20% of cesarean deliveries in the world IV acetaminophen warrants further investigation in patients not receive long-acting intrathecal opioids.

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