

A Randomized Controlled Trial of Intravenous and Intramuscular Ketorolac for Post-Cesarean Analgesia

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Abstract

Background: Optimal analgesia post-cesarean delivery is essential to promote maternal recovery for the care of the newborn. Intravenous (IV) ketorolac is commonly administered as a part of multi-modal analgesia for cesarean delivery. Ketorolac pharmacokinetics is altered in pregnancy. The purpose of this study is to compare the efficacy of IV and intramuscular (IM) ketorolac for post-cesarean analgesia.

Methods: This study is a prospective, double blinded, randomized controlled trial to assess the efficacy of IV versus IM ketorolac administration on post-cesarean analgesia. Patients undergoing an elective cesarean delivery under spinal anesthesia were randomized to receive either 30 mg IV ketorolac (Group 30IV), 30 mg IM ketorolac (Group 30IM), or 60 mg IM ketorolac (Group 60IM). Primary outcomes include time to the first analgesic, total analgesic consumption, and pain scores. Secondary outcomes include patient satisfaction, opioid related side effects, and length of hospital stay.

Results: The time to first break through pain was not statistically significant in the IM groups as compared to the IV group (Group 30IV 527 min, Group 30IM 578 min and Group 60IM 581 min). Pain scores and post-operative analgesic use did not differ significantly between groups. Secondary outcomes did not differ between groups.

Conclusions: IV and IM ketorolac are equally effective for post-cesarean analgesia.

Keywords: Analgesia obstetrical; Ketorolac; Cesarean delivery

Introduction

Cesarean delivery is the most frequently performed surgery in the United States. In order to promote maternal recovery so that the mother can care for her newborn, it is essential to optimize analgesia post-cesarean delivery. With the current opioid epidemic, multimodal analgesia is important to minimize opioid use post-operatively.

Current recommended multimodal analgesia for cesarean delivery includes intrathecal morphine, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen [1,2]. Ketorolac is the NSAID of choice for post-cesarean analgesia and is shown to provide effective post-cesarean analgesia when administered either intravenously (IV) or intramuscularly (IM) [3-7]. A meta-analysis including general surgical patients shows that 60 mg ketorolac had opioid sparing effects, whereas 30 mg ketorolac did not [8]. That meta-analysis also shows that 60 mg ketorolac has more opioid sparing effects when administered IM then when administered IV [8]. No studies, however, confirm this finding for cesarean delivery.

Pregnancy is associated with physiologic changes that affect the pharmacokinetics of medications [9]. These changes include increased total body water, increased hepatic and renal blood flow, decreased serum albumin, and altered hepatic metabolism [9]. In the immediate post-partum period, IV ketorolac pharmacokinetics are altered such that ketorolac clearance and volume of distribution are both increased [10,11].

Given the increased clearance of ketorolac in the immediate post-partum period, we hypothesized that IM ketorolac would provide improved analgesia as compared to IV ketorolac. Additionally, given the increased volume of distribution of ketorolac in the immediate post-partum period, we hypothesized that higher doses of ketorolac would provide better analgesia.

We sought to compare the analgesic efficacy of two different doses of IM ketorolac (60 mg or 30 mg) to that of IV ketorolac (30 mg) given as a single peri-operative dose for women undergoing a scheduled elective cesarean delivery.

Materials and Methods

Study design

We performed a single center, prospective, double blinded, randomized controlled trial to assess the effectiveness of IV versus IM ketorolac administration on post-operative pain control after cesarean delivery. The Institutional Review Board (IRB) and Henry Ford Hospital approved this study protocol (IRB #9635) on June 9, 2015. All study participants gave written informed consent that was approved by the IRB prior to enrolling in the study. The study is reported in accordance with the CONSORT statement guidelines.

Study population

From July 2015 through July 2017, all patients presenting to the labor and delivery unit at Henry Ford Hospital, which is an academic tertiary care hospital, for a scheduled cesarean delivery were assessed for eligibility. Inclusion criteria include all patients at term gestation scheduled to undergo an elective scheduled cesarean delivery under spinal anesthesia. Exclusion criteria include gestational age <37 weeks, chronic opioid use, a chronic pain or psychological disorder, history of allergic reaction to NSAIDs, peptic ulcer disease, history of gastrointestinal bleeding, renal failure, the planned use of either a combined spinal epidural anesthetic, epidural anesthetic, or general anesthetic, and a high risk for post-operative bleeding.

Study intervention

After obtaining written informed consent, the patients were randomized to receive either 30 mg IV ketorolac (Group 30IV), 30 mg IM ketorolac (Group 30IM), or 60 mg IM ketorolac (Group 60IM). All patients underwent a low transverse cesarean delivery under a standardized spinal anesthetic with 1.4 mL-1.6 mL, 0.75% bupivacaine, 8.25% dextrose, 15 mcg fentanyl, and 0.15 mg preservative free morphine. Upon completion of the surgical procedure, all patients received a 2 mL IV injection and a 2 mL IM injection in the anterolateral thigh. One of the injections contained the study medication and one of the injections contained saline based on the group assignment.

The patients were recovered and received routine post-partum care. The standard post-operative analgesic regimen for the first 24 h after spinal placement included ketorolac 30 mg IV every 6 h as needed for moderate pain (pain score of 4-6). IV or oral acetaminophen was ordered as needed by the obstetric team during the first 24 h if pain was not well controlled with IV ketorolac. After 24 h, the post-operative analgesic regimen included 600 mg oral ibuprofen every 6 h as needed for mild pain (pain score of 1-3) and hydrocodone-acetaminophen 5-325, 1-2 tablets, every 4 h as needed for moderate pain (pain score of 4-6).

Study outcomes

Primary outcomes include time to the first analgesic, total analgesic consumption as measured every 24 h for the first 48 h post-operatively, and worst pain scores at 4 h, 8 h, and 24 h post-operatively as measured with the numeric rating scale (NRS) ranging from 0-10. On this NRS, 0 represents no pain, 1-3 represents mild pain, 4-6 represents moderate pain, and 7-10 represents severe pain [12]. Total analgesic consumption was analyzed as total acetaminophen, ketorolac, ibuprofen, and oral morphine equivalents at each 24 h time frame.

Secondary outcomes include patient satisfaction as measured on a 3 point scale (very satisfied, satisfied, and not satisfied), presence or absence of opioid related side effect of nausea and vomiting as measured by the use of antiemetic medication, and length of hospital stay as measured by the day of hospital discharge.

Sample size

The meta-analysis by De Oliveira et al., shows that IM ketorolac significantly decreases post-operative opioid consumption by a mean

of 2.13 mg of IV morphine equivalents as compared to IV ketorolac [8]. This decrease in opioid consumption translates to approximately a 10-20% decrease in opioid consumption. We anticipated a small effect size in primary and secondary outcomes. We determined that 50 patients in each group would be needed to detect an effect size of 0.056 with an alpha less than 0.05 and a power greater than 80%.

Randomization and blinding

A biostatistician not involved with the study design or implementation created a computer generated randomized group assignment with a 1:1:1 group allocation for each sequential patient. The research pharmacy used the sequential patient list with group randomization assignments to prepare the study medications. Based on the randomized group assignment, the research pharmacy prepared two syringes for each patient labeled as INV-Placebo/Ketorolac (IRB 9635) IV injection 2 mL and INV-Placebo/Ketorolac 30/60 mg (IRB 9635) IM injection 2 mL. These syringes were hand delivered to the anesthesia provider. All patients, anesthesia providers, obstetricians, study personal, and data analysts remained blinded to group assignment throughout the duration of the study. Once enrollment and data collection was complete, the research pharmacist provided the study team with the randomization list.

Statistical methods

Baseline demographics for each group are presented as frequency (%) and mean (standard deviation) as appropriate. The primary outcome of time to the first breakthrough analgesic was analyzed using ANOVA to compare the log-normal time distribution between each group. ANOVA was used to analyze the total analgesic consumption between groups. Pain scores were categorized into mild to no pain (NRS<4) or moderate to severe pain (NRS ≥ 4) at all-time points. A chi squared test was performed to compare the categorized pain scores in each group. The secondary outcome of antiemetic use was analyzed using a chi square test comparing whether or not the patient received an antiemetic medication. Chi squared was used to analyze patient satisfaction on a 3 point scale.

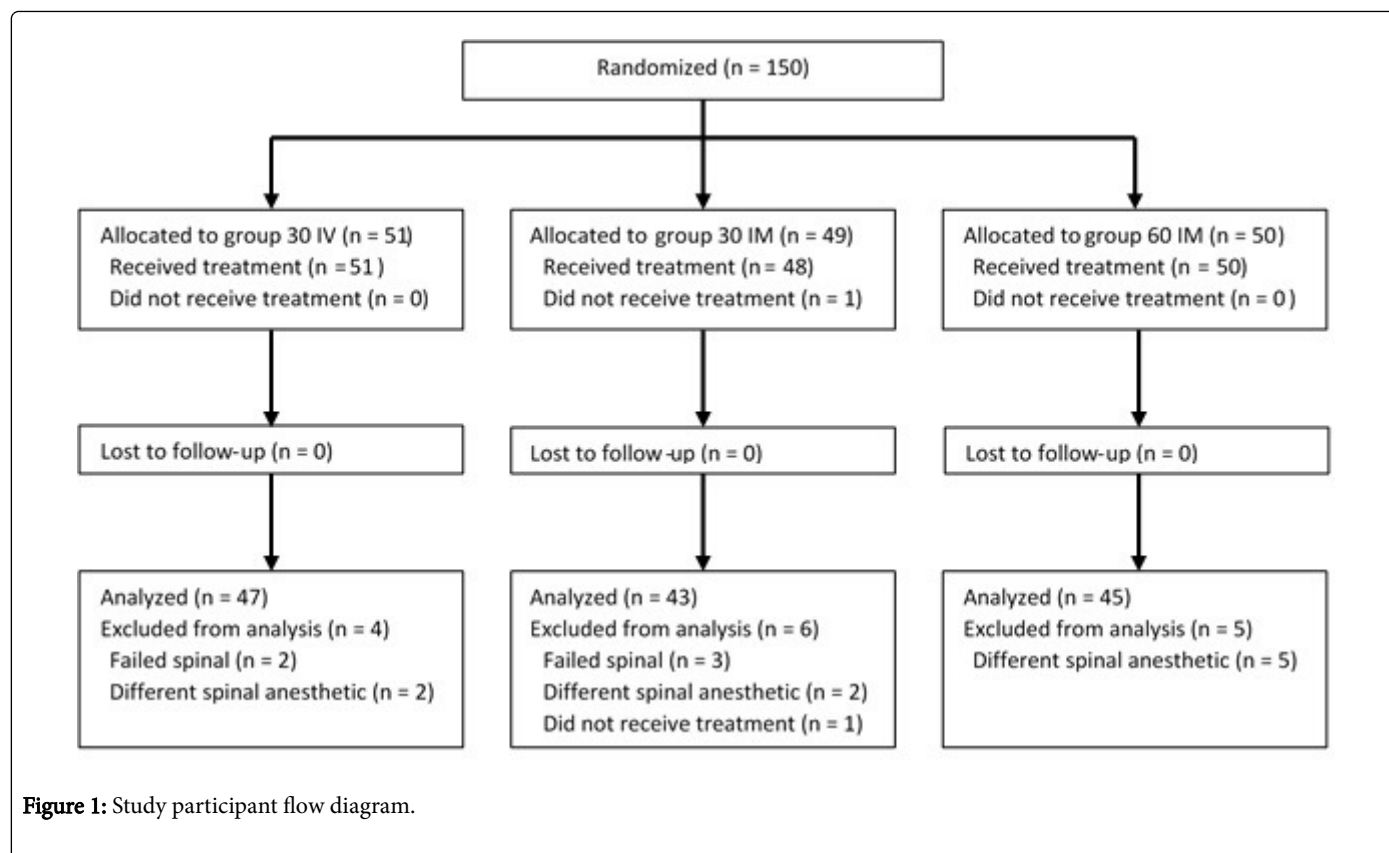
Results

Study population

From July 2015 through July 2017, 150 patients presenting the labor and delivery for an elective cesarean section met inclusion criteria, consented to participate in this study, and were randomized. After randomization, 15 patients were excluded from analysis. Of these patients, 5 patients had a failed spinal anesthetic, 9 patients required a spinal anesthetic plan that differed from the standard protocol in this study, and 1 patient did not receive the study medication. In total, 135 patients were included in the analysis: 47 in group 30IV, 43 in group 30IM, and 45 in group 60IM (Figure 1).

Baseline demographics

Patient demographic information did not differ significantly between groups (Table 1). Duration of surgery was similar between groups.

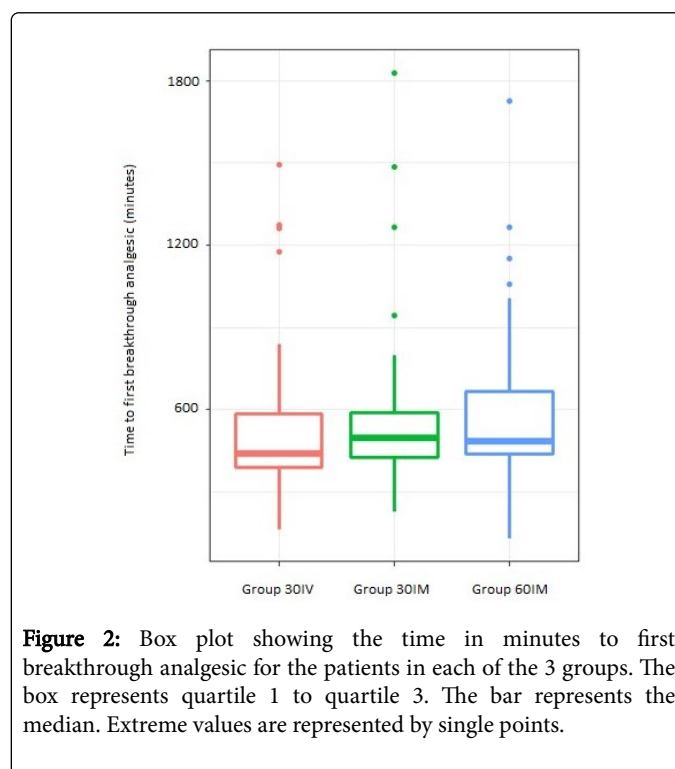


	Group 30IV (n=47)	Group 30IM (n=43)	Group 60IM (n=45)
Maternal Age	29.5 (5.4)	30.6 (5.3)	29.5 (6.3)
Body Mass Index (kg/m ²)	34.1 (7.1)	32.5 (5.7)	34.8 (7.7)
Gestational age (weeks)	38.7 (1.0)	39 (0.9)	38.7 (1.3)
Parity			
Nulliparous (P=0)	2 (4.3)	1 (2.3)	3 (6.7)
Primiparous (P=1)	8 (17.0)	13 (30.2)	18 (40.0)
Multiparous (P ≥ 2)	34 (72.3)	25 (58.1)	21 (46.7)
Grand Multiparous (P ≥ 5)	3 (6.4)	4 (9.3)	3 (6.7)
Surgical Duration (min)	79.4 (19.7)	75.7 (19.0)	77 (24.6)

Table 1: Demographic Data. Age, body mass index, gestational age, and surgical duration are reported as mean (standard deviation). Parity is reported as count (percent). Surgical duration is the time from spinal placement to study drug administration. P values are not significant and are not reported.

Primary outcome

The mean time to the first breakthrough analgesic is not statistically different between the IM groups 30IM (578 min) and 60IM (581 min) and the IV group 30IV (527 min) (Figure 2).



The total post-operative analgesic usage during the first 24 h post-operatively did not differ significantly between groups (Table 2). During the second 24 h post-operatively, group 30IM has a mean

consumption of oral morphine equivalents (29 mg) that is lower than that of groups 30IV (38 mg) and 60IM (36 mg) ($p=0.009$). However, when we control for the false discovery rate because we are testing multiple hypotheses simultaneously, the difference in oral morphine equivalents at 24-48 h does not reach the threshold for significance ($p=0.08$). Worst pain scores at 4 h, 8 h, and 24 h did not differ significantly between groups (Table 3).

	Group 30IV (n=47)	Group 30IM (n=43)	Group 60IM (n=45)	
Analgesic use 0–24 h				
Acetaminophen (mg)	379 (724)	215 (556)	307 (688)	$p=0.87$
Ibuprofen (mg)	40 (151)	29 (131)	41 (153)	$p=0.92$
Ketorolac (mg)	74 (23)	70 (25)	72 (29)	$p=0.91$
Oral morphine equivalents (mg)	2 (4)	1 (3)	2 (4)	$p=0.87$
Analgesic use 24–48 h				
Acetaminophen (mg)	2345 (730)	1967 (926)	2239 (792)	$p=0.34$
Ibuprofen (mg)	1296 (615)	1214 (593)	1347 (679)	$p=0.87$
Ketorolac (mg)	8 (13)	9 (18)	5 (12)	$p=0.87$
Oral morphine equivalents (mg)	38 (11)	29 (14)	36 (14)	$p=0.08$

Table 2: Total analgesic consumption. The acetaminophen, ibuprofen, ketorolac, and oral morphine equivalents consumed in the time frames of 0–24 h and 24–48 h are reported as mean (standard deviation).

	Group 30IV (n=47)	Group 30IM (n=43)	Group 60IM (n=45)	
Pain score at 4 h				
VAS<4	29 (61.7)	23 (53.5)	28 (62.2)	$p=0.646$
VAS ≥ 4	18 (38.3)	20 (46.5)	17 (37.8)	
Pain score at 8 h				
VAS<4	26 (55.3)	21 (48.8)	31 (68.9)	$p=0.149$
VAS ≥ 4	21 (44.7)	22 (51.2)	14 (31.1)	
Pain score at 24 h				
VAS<4	15 (31.9)	19 (44.2)	22 (48.9)	$p=0.232$
VAS ≥ 4	32 (68.1)	24 (55.8)	23 (51.1)	

Table 3: Pain scores at 4, 8, and 24 h after cesarean delivery. Data are presented as count (percent).

Secondary outcomes

The use of antiemetic medication did not differ significantly between groups. Patient satisfaction and length of hospital stay did not differ significantly between groups (Table 4).

	Group 30IV (n=47)	Group 30IM (n=43)	Group 60IM (n=45)	
Patient Satisfaction				$p=0.569$
Very satisfied	42 (89.4)	41 (95.3)	41 (91.1)	
Satisfied	5 (10.6)	2 (4.7)	4 (8.9)	
Not satisfied	0 (0)	0 (0)	0 (0)	
Antiemetic medication				$p=0.638$
Patient received	8 (17.0)	9 (20.9)	6 (13.3)	
Patient did not receive	39 (83.0)	34 (79.1)	39 (86.7)	
Day of Discharge				$p=0.455$
POD #2	22 (46.8)	27 (62.8)	25 (55.5)	
POD #3	23 (48.9)	14 (32.6)	17 (37.8)	
POD #4	2 (4.3)	1 (2.3)	3 (6.7)	
POD #5	0 (0)	1 (2.3)	0 (0)	

Table 4: Secondary outcomes. Data are presented as count (percent).

Discussion

Based on our study, IM and IV ketorolac given as a single peri-operative dose are equally effective for relieving maternal pain after cesarean section.

De Oliveira et al., performed a meta-analysis of 13 randomized controlled trials to assess the effectiveness of a single peri-operative dose of ketorolac on post-operative pain and opioid consumption in the general surgical population [8]. They found evidence that a single 60 mg ketorolac dose reduces post-operative pain and opioid consumption; however, they could not find evidence for a benefit from a single 30 mg ketorolac dose. However, this meta-analysis may have been too underpowered to detect a benefit [13]. This meta-analysis also suggests an increased opioid sparing effect from 60 mg IM ketorolac as compared to 60 mg IV ketorolac. Common clinical practice is the administration of a single peri-operative 30 mg IV ketorolac dose. Based on the meta-analysis by De Oliveira et al., this practice may not have the most benefit.

Several studies demonstrate that both IM [3,6] and IV [4,5,7] ketorolac are effective in decreasing opioid consumption after cesarean delivery. As far as we are aware, this study is the first to compare a single peri-operative dose of IM and IV ketorolac for post-operative analgesia after cesarean delivery.

Ketorolac is highly protein bound, has a limited volume of distribution, and has a terminal half-life of approximately 5-6 h regardless of the route of administration [14]. When given IM, the bioavailability of ketorolac approaches 100% and the time to peak concentration (C_{max}) is 45-50 min [15-17]. When given IV, the C_{max} is considerably shorter at 5-6 min [15,17]. The area under the curve (AUC) for serum ketorolac concentration over time when ketorolac is given IV is about 93% the AUC of an equivalent dose given IM [15]. These pharmacokinetic differences between the IM and IV route may explain the clinical differences in pain control seen in the meta-analysis by De Oliveira et al.

Pregnancy is associated with physiologic changes that can affect the pharmacokinetics of ketorolac [9]. Several studies investigate the pharmacokinetics of IV ketorolac [10,11,18]. Ketorolac clearance at the time of cesarean delivery is nearly twice that in non-pregnant women (2.11 and 1.07 L/h/m², respectively) [11]. The volume of distribution of ketorolac at the time of cesarean delivery is also increased as compared to non-pregnant women (0.24 and 0.17 L/kg, respectively) [11]. Since ketorolac is highly protein bound, the higher volume of distribution at the time of cesarean delivery suggests an increase in the unbound ketorolac due to hypoalbuminemia of pregnancy. The increased volume of distribution due to unbound drug may explain the increase in ketorolac clearance since ketorolac is mainly cleared through renal elimination. Ketorolac is also metabolized through oxidation and glucuronidation. On examining urinary ketorolac metabolites, Allegaert et al. show that the increase in ketorolac clearance at the time of delivery is in part related to increased ketorolac oxidation [10]. Additionally, the S enantiomer that is responsible for ketorolac analgesia has a higher clearance than the R enantiomer at the time of delivery [18].

The increased clearance of IV ketorolac at the time of delivery suggests that the analgesic effect of the medication may not last as long after a cesarean delivery as it would after general surgery. Additionally, the increased volume of distribution suggests that higher doses may be needed for patients undergoing cesarean delivery to achieve analgesia. On the other hand, hypoalbuminemia of pregnancy would result in a higher concentration of unbound ketorolac since this drug is highly protein bound. Since analgesia is related to the concentration of unbound drug [9] the analgesic efficacy may be improved in the immediate post-partum period.

We hypothesized the pharmacokinetic differences between IM and IV doses in non-pregnant volunteers might be accentuated in pregnant women at the time of cesarean delivery. As such, we anticipated that IM ketorolac dosing would provide better analgesia and allow for delayed time to first breakthrough analgesia. Although not statistically significant, the mean time to first breakthrough analgesic was longer in 30IM and 60IM than in 30IV by 51 and 54 min respectively. This difference is consistent with longer C_{max} seen with IM ketorolac dosing in non-pregnant volunteers. While including more patients might have made this difference statistically significant, the clinical significance of a 50 min increase in time to first breakthrough analgesic is unclear.

Based on the pharmacokinetic studies in pregnant patients undergoing cesarean delivery, we hypothesized that higher doses of ketorolac would be needed to provide analgesia. We did not see a difference in our results. Pain scores and total analgesic consumption were not different between groups. Our results suggest that higher doses of ketorolac do not provide superior pain relief for patients undergoing cesarean delivery.

Our hypothesis was based on the fact that pregnancy results in both an increased volume of distribution of ketorolac and an increased ketorolac clearance. However, our results do not confirm our hypothesis. Therefore, the concomitant hypoalbuminemia of pregnancy and the subsequent increase in free ketorolac may equally balance the effect of the increased volume of distribution and increased clearance.

There are several limitations to this study. First, several patients (10%) were excluded post randomization. The majority of these patients were excluded because the patient required an anesthetic that

differed from the study protocol as determined by the primary anesthesiologist. It is possible that if fewer patients were excluded, the study may have been adequately powered to detect a difference in the time to first breakthrough analgesic.

Second, the post-partum nurses were not aware that the patients were enrolled in this study. As such, pain scores were not required to be reported at the time of analgesic administration. All patients enrolled in the study had the standard post-cesarean analgesia order set that included ketorolac for the first 24 h followed by ibuprofen and a combined oral opioid-acetaminophen analgesic based on the patients' pain scores. Since we did not require pain scores to be recorded at the time of analgesic administration, analgesic medications may have been given prophylactically instead of only when the patient expressed pain. If medications were given preemptively, our broad similarity in analgesic consumption between groups may be reflective of the standard nursing practices on our post-partum floor and may not be affected by the peri-operative ketorolac dose.

Conclusion

In conclusion, our study suggests that IM or IV ketorolac as a single dose at the time of cesarean delivery provide equal analgesia as measured by pain scores, opioid consumption, maternal satisfaction, and opioid related side effects. Because IV injection is less painful than IM injection, we recommend 30 mg IV ketorolac for post-cesarean analgesia as both are equally effective.

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