A Randomized Double-Blind Comparison of IV Ibuprofen vs. IV Ketorolac to Prevent Postoperative Pain after Scheduled Cesarean Section

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Abstract

Introduction: Intravenous ibuprofen may offer advantages over ketorolac for postoperative pain control, perioperative bleeding, and secretion into breast milk. This study examined analgesia after Cesarean section and perioperative Cesarean section bleeding, comparing intravenous ibuprofen to intravenous ketorolac. **Methods:** Forty-eight patients received in randomized, double-blinded fashion, 4 doses of either IV ibuprofen or IV ketorolac every 6 hours beginning just after scheduled primary or repeat Cesarean section conducted with bupivacaine spinal anesthesia. Rescue, on demand hydromorphone via a patient controlled analgesia pump measured unmet analgesic need. Drop in serum hemoglobin concentration assessed clinically relevant bleeding. **Results:** The demographically similar groups (33±4.8 [SD] years old; 64±2.7 inches tall; 92±20.8 kg weight) did not differ in perioperative fluid administration or operative time. The numbers of hydromorphone doses requested did not differ (5.04 ± 6.49 [median 3] for ketorolac; 7.92 ± 10.43 [4] for ibuprofen; P= 0.56) nor did those delivered (4.30 ± 4.85 [3] vs. 6.96 ± 9.17 [4] respectively; P=0.59). No patient received a transfusion. Perioperative decrease in hemoglobin concentration did not differ (1.99 ± 0.66 [2.0] ketorolac vs. 2.26 ± 0.91 [2.1] ibuprofen, P=0.35). **Discussion:** IV ibuprofen appears to offer no analgesic or bleeding-related benefit over IV ketorolac in patients undergoing scheduled primary or repeat Cesarean section.

Introduction

Uncontrolled postoperative pain, often unpleasant and exhausting for patients, can also cause hypertension and tachycardia, leading to unnecessary further testing and/or therapeutic interventions. In postpartum patients, infant-mother separation and delayed initiation of breastfeeding may ensue. Intravenous (IV) non-steroidal anti-inflammatory drugs (NSAIDs) form a key component of multi-modal treatment for post-operative pain. Their peripheral anti-inflammatory effects may augment their analgesic effects. IV ibuprofen has joined IV ketorolac in the physician's armamentarium of IV NSAIDs. Controlled studies have documented the efficacy and safety of an infusion of IV ibuprofen.[1]

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Ketorolac and ibuprofen differ in their inhibitory effects on cyclooxygenase (COX), isoforms 1, 2 and 3 of which are found throughout the body and play a role in pain transduction, inflammation, fever, coagulation, and GI mucosal protection.[2] Both COX-1, expressed in platelets and GI mucosa, and COX-2, found in skeletal, smooth, and cardiac muscle, convert arachidonic acid to prostaglandin, transducing pain and inciting inflammation. Inhibition of COX-1, however, also results in inhibition of platelet aggregation and reduced GI mucosal protection, both undesirable sequelae.[3] Ibuprofen features a COX-1 to COX-2 inhibition ratio of approximately 2.5:1.[4] Ketorolac has less COX-2 selectivity than ibuprofen, resulting in a theoretically higher risk for bleeding. For example, the Health Canada Product Monograph contraindicates ketorolac (1) immediately before and during major surgery "when hemostasis is critical"; (2) in postoperative patients with high hemorrhagic risk; (3) in patients with coagulation disorders; and (4) in delivery "because, through its prostaglandin synthesis inhibitory effect, it may…inhibit uterine musculature, thus increasing the risk of uterine hemorrhage."[5]

Previous IV ibuprofen trials have featured both preoperative and postoperative dosing.[6-9] Available information indicates less concern for perioperative bleeding with ibuprofen. For example, the Health Canada Product Monograph contraindicates intravenous ibuprofen for cardiac surgery only.[10] Still, ketorolac enjoys wide perioperative use. However, IV ibuprofen enters a perioperative environment well-accustomed to ketorolac. To switch usage from ketorolac to ibuprofen, clinicians need evidence of superior analgesic properties, less perioperative bleeding, or both.

This trial sought to determine whether or not patients for scheduled primary or repeat Caesarean section who receive post-operative IV ibuprofen, compared to those receiving IV ketorolac, would need less rescue analgesia, provided with hydromorphone. It also examined changes in hemoglobin concentrations to quantify postoperative bleeding accompanying use of the two agents.

Methods

With approval of the Institutional Review Board, all women scheduled for primary or repeat Cesarean sections at a single institution were screened for participation. Those excluded had allergy to any NSAID or hydromorphone; renal dysfunction including severe preeclampsia; hepatic dysfunction; gastrointestinal ulcers, bleeding, or perforation; or poorly controlled asthma. All patients provided written, informed consent. Randomization occurred via standard computer-based, pseudo-random number generation using opaque sealed envelopes, under supervision of the Director of Pharmacy. Group allocation remained concealed to all participants, healthcare providers, and data collectors until after study conclusion and database lock. The IRB did not require web-registration of this single-institution trial comparing two marketed products.

All patients underwent lumbar subarachnoid block in the sitting position with bupivacaine 12.5 mg, fentanyl 10 mcg, and morphine sulfate 0.2 mg, and no other intra-operative analgesic medication. They remained sitting for 2 min following intrathecal injection to achieve a minimum T6 analgesia level, measured 10 min later. All patients received intravenous hydration prior to placement of the subarachnoid block, and replacement of intra-operative losses with a balanced electrolyte, clear intravenous fluid calculated at approximately three times estimated blood loss.

Patients received either 30 mg ketorolac or 800 mg ibuprofen diluted in 200 mL NaCl in double-blind, randomized fashion, administered over 30 min, in the post-anesthesia care unit, started within 30 min of skin closure, followed by 3 additional doses every 6 hours. Patients received instructions to request rescue analgesia via a patient-controlled analgesia pump (PCA) containing hydromorphone with 0.2 mg per delivered dose, with a 10 min lockout and a maximum dose of 1.2 mg/h. Study patients received no analgesic medications except the randomized, blinded study drug and rescue hydromorphone. Hemoglobin concentrations were recorded preoperatively and again on postoperative day 1.

The Fisher exact test compared frequency data, while the unpaired Student's t-test compared continuous data, unless not normally distributed, in which case the Wilcoxon rank-sum test was used. Nominal significance levels are reported for demographic data. The primary outcome efficacy variable for estimating sample size was the number of PCA requests.

Based on several years' experience using ketorolac in an obstetric setting, the investigators expected approximately 5±4 (SD) delivered doses of PCA hydromorphone over 24h in that group. A clinically relevant improvement would halve that value. With an expected variance of 16 and a 5% type I error, a difference of 3 delivered doses can be detected with 80% power using 29 patients per group. To account for dropouts, we elected to study a total of 60 patients.

For the safety outcome variable, decrease in hemoglobin concentration, a review of clinical records estimated the standard deviation at 0.9 g/dL. The 29 patients per group, determined for the primary outcome variable, provide 90% power to detect a clinically relevant 0.78 g/dL difference between treatment groups for this secondary, safety outcome. Each comparison, primary efficacy and safety, required a two-sided nominal significance level <0.05 to achieve statistical significance. The number of delivered PCA doses constituted a secondary efficacy outcome, tested hierarchically only if the primary efficacy outcome, PCA requested doses, achieved statistical significance, to preserve the family-wise alpha.

Results

Of the 60 enrolled and randomized patients, 48 had rescue analgesia data collected: 4 withdrew consent prior to study drug administration, thus requiring an analgesic regimen other than rescue PCA hydromorphone; surgeons for 3 other patients directed open-label ketorolac instead of study medication; 2 patients experienced intraoperative hemorrhage, contraindicating NSAID administration's the PCA pumps malfunctioned in 2 patients, providing no data; and 1 patient developed perioperative severe preeclampsia prior to study medication administration (Figure 1). Of the 48 patients with outcome data, 25 received ibuprofen and 23 received ketorolac. Groups did not differ in either demographic characteristics or perioperative variables of interest (Table 1). Although pre-operative hematocrit barely escaped nominal statistical significance, an absolute hematocrit difference of 1.8% carries no clinical significance.

Neither the number of PCA requests (P=0.56) nor the number of hydromorphone doses delivered (P=0.59) differed between the two groups (Table 2). Perioperative decreases in hemoglobin concentration also did not differ between groups. For both the efficacy and safety outcomes, the mean values in the ibuprofen group were numerically higher, whereas the study hypotheses would require each to be numerically lower. There were no drug-related adverse effects recorded for any patient during the study period, including allergic reactions, GI ulcers, or GI perforations.

Discussion

This randomized, double blind study of two approved medications for post-Cesarean section analgesia failed to demonstrate an analgesic advantage of ibuprofen over ketorolac. Postoperative hemoglobin concentrations also did not differ, refuting the theoretical concern of increased bleeding with ketorolac.

This study obtained only 48 patients with data for analysis out of its intended 58, suggesting that its failure to show a superiority of ibuprofen might arise from inadequate statistical power. However, results trended in the opposite direction: patients who received ibuprofen logged more PCA attempts (7.9 vs 5.0 mean; 4 vs 3 median) and more PCA delivered doses (7.0 vs 4.3 mean; 4 vs 3 median) than those who received ketorolac. Even if all 4 missing patients in the ibuprofen arm requested and received zero PCA doses, and all 6 missing patients in the ketorolac arm requested 16 and received 13 doses (the corresponding 95th percentile values of the 21 ketorolac subjects), the number of requested doses would be 6.8 ± 10.1 (median 2) for ibuprofen vs 7.3 ± 7.3 (median 5) for ketorolac (P=0.34 by Wilcoxon test), and the number of delivered doses would be 6.0 ± 8.8 (median 2) for ibuprofen vs 6.1 ± 5.6 (median 5) for ketorolac (P=0.35 by Wilcoxon test). Likewise, imputing no decrement in hemoglobin concentration for 4 additional ibuprofen subjects and a 2.9 g/dL decrease (the ketorolac group 95th percentile value) for each of 6 additional ketorolac subjects yields decreases of 1.9 ± 1.2 for ibuprofen subjects and 2.2 ± 0.7 for ketorolac subjects (P=0.38 by Wilcoxon test). Even were it statistically significant, an 0.3 g/dL difference of imputed means remains clinically irrelevant. This futility-type sensitivity analysis argues against repeating this study with the full sample size.

Other limitations of this study include recruitment from a single institution, which limits generalizability, and the potential for confounding effects of repeat Cesarean procedures, which may entail more extensive dissection, increased post-operative pain, and more perioperative bleeding. However, the groups were balanced for the number undergoing repeat procedures: 18 in the ibuprofen group (72%) and 19 in the ketorolac group (83%). The current study also offers no insight regarding a third major issue determining choice of postoperative analgesic after Cesarean section: breast-feeding.

Postpartum NSAID use raises concern over inadvertent neonatal exposure via breast milk. NSAIDs may inhibit physiologic closure of the neonatal ductus arteriosus. Both the United States Prescribing Information[11] and the Health Canada Product Monograph[5] for ketorolac contraindicate its use in nursing mothers, based on the potential adverse effects of prostaglandin-inhibiting drugs on neonates. However, clinical trials have demonstrated low ratios of milk to plasma ketorolac following oral administration of 10 mg ketorolac (0.037), and after 4 oral doses over 1 day (0.025),[12,13] with maximum milk concentrations of 7.9 ng/mL of ketorolac in the latter case.[5] This calculated infant exposure ranges between 0.16% and 0.40% of the maternal dose,[12] which is well within the 10% threshold considered safe. Notably, the American Association of Pediatrics finds ketorolac compatible with breastfeeding.[13]

Regarding IV ibuprofen, the Health Canada Product Monograph contraindicates it in women who are breastfeeding,[10] while the United States Product Information urges use with caution in lactating women, based on a lack of studies measuring IV ibuprofen secretion in human milk.[4] Studies with oral ibuprofen suggest a very small amount enters breast milk.[14]

This study failed to show a superiority of IV ibuprofen over IV ketorolac for postoperative pain relief. The concern for increased perioperative bleeding also influences the decision to use a post-operative non-opioid analgesic. Both NSAID drugs inhibit platelet aggregation by reversibly inhibiting COX-1. With the potential for less inhibition of uterine smooth muscle via COX-2 effects, ibuprofen could theoretically engender less bleeding compared to ketorolac. Despite the difference in COX-2 selectivity, no difference in hemoglobin concentration decrease was observed. This measure provides a reasonable inference on perioperative bleeding because (1) patients received appropriate intravenous hydration to replace intra-operative blood loss; (2) the timing of post-operative hemoglobin concentration determination allowed for equilibration of intra- and extravascular fluid spaces; and, (3) no patient received a red blood cell transfusion. In the absence of red cell transfusions, hemoglobin concentration change provides a suitable outcome to estimate perioperative blood loss, being more objective than estimates from soaked sponges and dressings and from suction canisters. If indicative of perioperative bleeding, point estimates of the decreases in hemoglobin concentration numerically favored less bleeding with ketorolac, the opposite of the hypothesized effect; the data indicate no significant difference between the groups.

The current study demonstrates no difference in postoperative analgesia provided parturients by these parenteral medications, nor a clinically meaningful difference in perioperative bleeding. Ketorolac currently features both an extensive safety record and a substantially lower (generic) cost compared to parenteral ibuprofen.[15] In breastfeeding patients, healthcare providers must balance these qualities against the off-label use of ketorolac and the theoretical potential for adverse neonate effects. Future investigations can compare parenteral acetaminophen, a non-NSAID analgesic, to either or both of the currently studied agents.

Table 1: Demographic data

Variable	Ketorolac n = 23	Ibuprofen n = 25	P
AGE	32 ± 5.8	33 ± 3.7	0.41
GRAVITY	2.8 ±1.58	2.6 ± 0.91	0.55
PARITY	1.2 ± 0.93	1.0 ± 0.53	0.55
HEIGHT (cm)	163 ± 7.54	163 ± 6.15	0.89
WEIGHT (kg)	90.2 ± 19.3	93.3 ± 22.4	0.60
Repeat operation	19	18	0.50 Fisher Exact
Pre-operative Hgb	11.4±1.16	12.1±1.14	0.02 Wilcoxon
Operative fluids (mL)	1572 ± 408	1656 ± 581	0.56
Operative time (min)	60.2 ± 21.6	59.1 ± 19.7	0.86

Entries are mean ± SD or numbers of patients. Hgb=hemoglobin (in g/dL). Comparisons by Student's t-test except where noted otherwise.

Table 2: Primary and secondary outcome variables

Variable	Ketorolac n = 23	Ibuprofen n = 25	Wilcoxon P
PCA attempts	5.04 ± 6.49 [3]	7.92 ± 10.43 [4]	0.56
PCA injections	4.30 ± 4.85 [3]	6.96 ± 9.17 [4]	0.59
Δ Hgb (g/dL)	1.99 ± 0.66 [2.0]	2.26 ± 0.91 [2.1]	0.35

Entries are mean ± SD [median]. PCA, patient controlled analgesia; Hgb, hemoglobin concentration
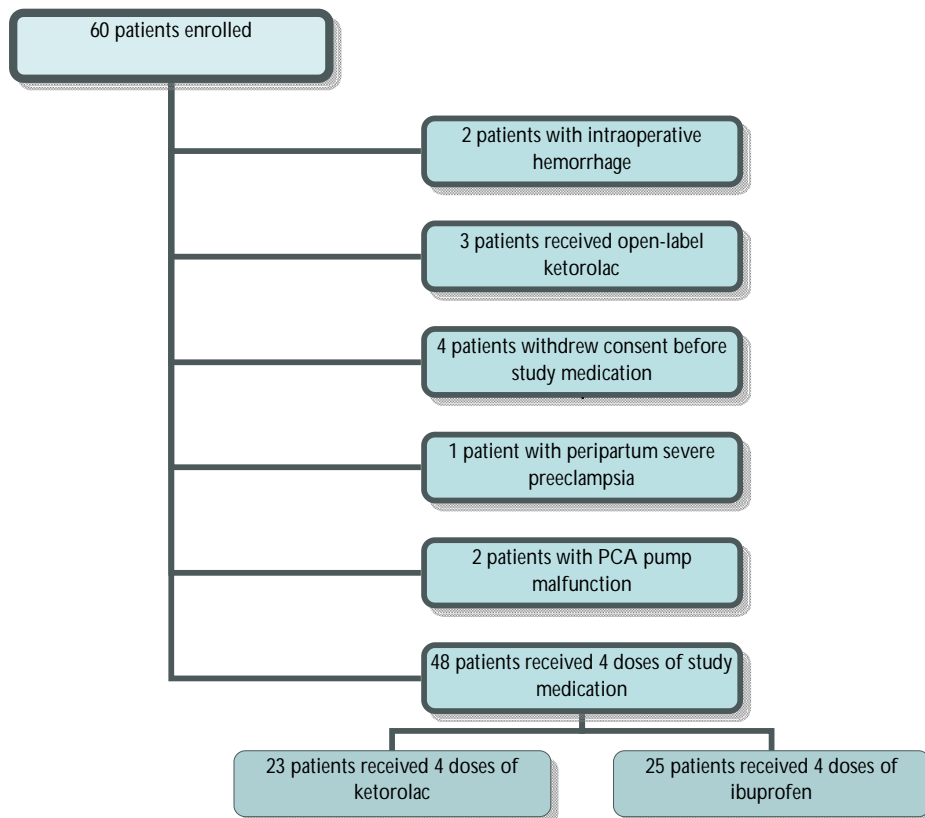

Figure 1: Consort diagram showing disposition of all patients enrolled. PCA, patient-controlled analgesia.

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