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Reducing Post Procedural Pain and Opioid Consumption Using IV Acetaminophen and IV Ibuprofen Following Uterine Fibroid Embolization: A Prospective, Double-blind, Randomized Controlled Study

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Abstract

Purpose: Uterine fibroid embolization (UFE) is associated with post-procedural pain and nausea. In this double-blind randomized controlled study, we compared pre-procedure intravenous (IV) acetaminophen/ibuprofen to post-procedure IV ketorolac in UFE patients.

Methods: After institutional review board approval, UFE candidates 21-60 years old were screened and randomly assigned to one of four arms: acetaminophen (1 g), ibuprofen (800 mg), acetaminophen (1 g) and ibuprofen (800 mg) combined, and an active comparator, ketorolac (30 mg). All received rescue patient-controlled hydromorphone for 24 h post-procedure. Primary outcome was measurement of pain intensity (visual analog scale: VAS) between the acetaminophen/ibuprofen group and the ketorolac group. The secondary outcomes were opioid and anti-emetic requirements and nausea intensity (VAS).

Results: 40 subjects were analysed: acetaminophen/ibuprofen (N=16); acetaminophen (N=4); ibuprofen (N=4); ketorolac (N=16). The maximum and mean VAS scores for pain were not different between the acetaminophen/ibuprofen group and the ketorolac group without adjusting for opioid consumption (p=0.243 and p=0.208, respectively). Total opioid consumption in morphine equivalents (mean [±SE]) was 28.09 mg (±4.58) in the acetaminophen/ibuprofen group and 40.33 mg (±7.79) in the ketorolac group (p=0.087), demonstrating a trend favouring the acetaminophen/ibuprofen group. The mean and maximum nausea scores showed a trend and significant difference (p=0.095 and p=0.003), respectively, favouring the ketorolac group.

Conclusion: IV acetaminophen/ibuprofen demonstrated comparable pain control, although there was less opioid requirement for the acetaminophen/ibuprofen group compared to the ketorolac group. Maximum nausea scores were significantly increased with similar ondansetron requirements. Therefore, antiemetic prophylaxis is needed regardless of group.

Keywords: Uterine Fibroid Embolization; Pain; Nausea; IV Acetaminophen; IV Ibuprofen; IV Ketorolac

Introduction

Over 70% of women develop fibroids [1], which may be associated with bulk symptoms such as urinary discomfort and pelvic pain, as well as excessive menstrual bleeding [2]. Symptomatic uterine fibroids are the most common etiology for hysterectomy in the United States [3]. A non-surgical, minimally invasive treatment option such as uterine fibroid embolization (UFE), however, has proven to be a successful alternative to hysterectomy [4,5]. UFE is associated with post-embolization syndrome, which includes post-procedure pain and nausea [6,7]. The etiology of the discomfort is explained by the resultant ischemia and inflammation of the myometrium following embolization [8]. Therefore, appropriate pain control is essential.

At the time this study was initiated, the standard of care to treat pain following UFE included the administration of oral or intravenous (IV) opioids and non-steroidal anti-inflammatory drugs (NSAID). Several options for post-procedural pain control have been suggested, many of which use opioid-based IV patient-controlled analgesia (PCA) with oral NSAIDs [9,10]. However, opioid-based therapy may result in dose-dependent side effects such as nausea, drowsiness, itching, sedation and respiratory depression [11]. To reduce these side effects, the World Health Organization and the American Society of Anesthesiologists recommend a multimodal foundation of acetaminophen and NSAIDs for management of pain, with opioids as a second tier treatment [12].

Oral pain medications are often difficult to administer in the early recovery period because in many cases, the patients are

sedated. Furthermore, the occurrence of nausea and vomiting following UFE can limit successful oral delivery of these needed pain medications. IV rather than oral forms of acetaminophen and NSAIDs avoid these issues and initiate early multimodal analgesia [13]. Thus, we designed a double-blind randomized controlled study comparing pre-emptive IV acetaminophen and/or IV ibuprofen to an active comparator (control), post-procedure IV ketorolac, to evaluate post-procedural pain and opioid requirement in UFE patients. Post-procedure nausea and antiemetic requirements were also evaluated.

Materials and Methods

Patients

Female UFE candidates of all ethnicities between 21 and 60 years of age were screened for eligibility. Patients with malignancy, pregnancy, cognitive impairment, clinically significant kidney and/or liver disease, gastrointestinal bleeding or ulcer, morbid obesity with body mass index (BMI) equal to or over 50, cardiac arrhythmias, or heart failure were excluded. Additionally, patients with known sensitivity to or chronic use of NSAIDs, acetaminophen, midazolam or fentanyl were also excluded from the study.

Study design

The patients were randomly assigned to 1 of 4 treatment arms. The 4 arms included: IV acetaminophen, IV ibuprofen, IV acetaminophen/IV ibuprofen, and IV ketorolac (control/active comparator). The sequence was generated by the block randomization of the treatment arms (with a ratio of 1:1:4:4) and the randomly assigned rankings using the uniform distribution. The identity of the study medication and placebo were blinded by the pharmacy. Thus, group allocation was blind to the patient, nurse coordinator, physicians, and nurses. The collected data were encrypted and were unlocked when 40 subjects completed the study. The random allocation sequence was generated by the statistician. Participants were enrolled by the primary investigator, and they were assigned to treatment arms by the study coordinator according to predetermined randomization.

The dosage of study drugs were standardized based on the FDA approved package insert: 1 g of IV acetaminophen was administered in the IV acetaminophen group, 800 mg of IV ibuprofen was administered in the IV ibuprofen group, 1 g of IV acetaminophen and 800 mg of IV ibuprofen were administered in the IV acetaminophen/ibuprofen group, and same volume of normal saline was administered in the control group. All study drugs and the saline for the control group were administered over 30 min as an IV infusion. The assigned study drugs were pre-emptively administered prior to the start of the procedure and for every 6 h for 24 h. For the control group (active comparator), a single IV injection of 30 mg ketorolac was administered at the end of procedure and then every 6 h for 24 h with a total dose of 120 mg/24 h due to Package Insert warning regarding potential bleeding with ketorolac. Conversely, a similar volume of normal saline was administered as a rapid IV infusion at the same time periods in the other 3 treatment arms. Each patient received a standardized IV PCA preparation of 10 mg of hydromorphone mixed in 50 mL of 0.9% saline for 24 h after the procedure. Each PCA self-administered dose was programmed at 1 mL or 0.2 mg of hydromorphone with a lock-out interval of 10 min (maximum 6 doses per hour). No basal continuous infusion was given *via* the IV PCA. The patients were advised and encouraged to press the PCA button as needed for pain control. Ondansetron was administered in 4 mg or 8 mg rapid IV infusions when the subject complained of nausea.

Uterine fibroid embolization

In the procedure room, routine monitors including electrocardiography (ECG), non-invasive blood pressure cuff, and a pulse oximeter probe applied to the patient. The patients were treated with a single dose of ciprofloxacin 400 mg IV and metronidazole 500 mg IV. Every patient received IV moderate sedation (1 mg of midazolam and 50 µg of fentanyl) with supplemental doses of midazolam and fentanyl given during the procedure when the subject complained of pain or anxiety. The level of consciousness during the procedure was maintained at a Ramsay sedation scale of 3 or 4 [14]. The entry site for the UFE procedures was the right femoral artery using a retrograde approach. Under fluoroscopic guidance, a 5.0-F macro catheter was inserted into the origins of the uterine arteries. Then a 3.0-F coaxial micro catheter was further advanced into these arteries and the macro catheter was retracted out of the origin of the uterine arteries. After confirmation of satisfactory positioning, 500-700 µm trisacryl gelatin microspheres (Embosphere®, Merit, South Jordan, UT) were injected. After the procedure, the catheter and sheath were removed and pressure was applied for haemostasis. The subject was then transported to a recovery area and eventually to an outpatient second stage recovery unit.

Data collection and outcome variables

The demographic variables of each subject included age, height, weight, body mass index (BMI), and race/ethnicity. Past medical and surgical history of the subjects was collected, including American Society of Anaesthesiologists (ASA) physical status classification **(Table 1)**. The uterine fibroid and procedure characteristics included diagnosis (fibroid or adenomyosis), size of the dominant fibroid, quantification of extent of fibroids, number and type of arteries embolized, total volume of particles injected and total administered doses of midazolam and fentanyl were collected **(Table 2).**

Table 1: Baseline characteristics of the study groups. The values are presented as mean (±SD) or absolute numbers.

	IV acetaminophen/IV ibuprofen (N=16)	IV ketorolac (N=16)
Age (yr)	44.33±4.32	44.49±4.12
Height (cm)	163.29±8.13	164.61±6.16
Weight (kg)	70.72±14.58	71.66±11.03
BMI	26.62±6.00	26.65±5.06

ASA grade (1/2/3/NA)	2/12/1/1	3/12/0/1
Hemoglobin (g/dL)	12.31±1.79	12.29±1.71

(All p-values of the baseline characteristics>0.05)

Table 2: Demographic information: Uterine fibroid and procedure characteristics.

	IV acetaminophen/IV ibuprofen (N=16)	IV ketorolac (N=16)
Uterine size in MRI (cm)	12.87±3.60	14.50±4.60
Diagnosis: fibroids/ adenomyosis	14/2	15/1
Dominant fibroid size (cm)	7.39±2.92	9.43±3.96
Quantification of fibroids: 1/2 - 5/>5	3/4/2009	3/6/2007
Total volume of Embospheres® (mL)	9.28±5.55	9.34±6.32
Total volume of fentanyl (µg)	170.3±66.6	206.3±89.2
Total volume of midazolam (mg)	2.66±1.18	2.94±0.98

The values are presented as mean (±SD) or absolute numbers.

(All p-values of the demographic information>0.05)

The primary outcome variables were maximum and mean pain intensity scores (VAS every 6 h for 24 h) comparing the acetaminophen/ibuprofen group and the ketorolac (active comparator/control) group [15,16]. The mean pain intensity and mean nausea scores were the scores present at exactly 6, 12, 18, and 24 h, while the maximum pain intensity and maximum nausea scores were the maximum score present during the entire interval from 0-6 h, 6-12 h, 12-18 h, and 18-24 h. The secondary outcomes were post-procedure opioid consumption (in morphine equivalents), mean and maximum nausea scores (VAS every 6 h for 24 h), and ondansetron consumption. Post-procedure complications and adverse events were recorded and classified into five grades according to the Common Terminology Criteria for Adverse Events (CTCAE) [17].

Statistical analysis

Descriptive statistics were reported by treatment arm for demographics and uterine characteristics (eg. size of dominant fibroid and length of uterus). A mixed-effects linear regression model was used to test the difference in the changes in pain intensities between the acetaminophen/ibuprofen group and the ketorolac group with adjusting the covariates of total opioid consumption and baseline pain scores. Each subject's longitudinal pain score contributes every 6 h of follow-up from the baseline using a random intercept/slope model. Two-sample Wilcoxon rank-sum tests were used to test the sum of mean VAS pain scores during the 24 h between acetaminophen/ibuprofen group and the ketorolac group, as well as to test total opioid consumption. Similarly, mixed-effects models were used to compare the longitudinal changes in the mean nausea scores using mixed-effect models with adjusting baseline nausea scores and requirement for ondansetron.

Results

Subject characteristics

Fifty-five patients were screened for eligibility, and a total of 43 subjects were consented and enrolled from October 2014 to April 2016. During the study, three subjects were withdrawn: one due to incomplete data collection and two declined to participate during the 24 h post-procedure. Demographic and baseline characteristics were recorded and analyzed. As a consequence, a total of 40 subjects completed the study: 4 in the IV acetaminophen group, 4 in the IV ibuprofen group, 16 in the IV acetaminophen/ibuprofen, and 16 in the active comparator ketorolac group (control) **(Figure 1)**. The baseline characteristics of the study groups are shown in **(Table 1)**, and the demographic information is summarized in (Table 2). There were no significant differences in baseline characteristics, uterine fibroid data, or procedure characteristics between the groups.

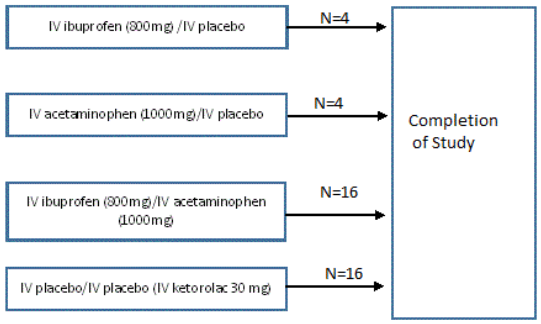

Figure 1: Flow diagram of subject treatment arms.

Outcome Measures

Mean and maximum VAS pain scores were not different between the IV acetaminophen/ibuprofen and the IV ketorolac group, adjusting for total opioid consumption (Figure 2: p=0.208 and p=0.243, respectively). Total sum of opioid consumption in morphine equivalents (mean [±SE]) was 28.09 mg (±4.58) in the acetaminophen/ibuprofen group and 40.33 mg (±7.79) in the control group (p=0.087), demonstrating a trend favouring the IV acetaminophen/ibuprofen group **(Figure 3)**.

The mean and maximum nausea scores demonstrated a trend and significant difference, respectively, favouring the ketorolac group (mean [±SE]) 1.23 (±0.73); p=0.095 and 2.35 (±0.79); p=0.003, adjusting for baseline nausea scores and the consumption of ondansetron **(Figure 4)**.

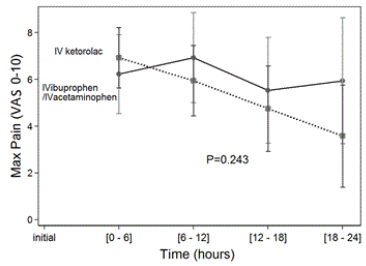

Figure 2: The maximum VAS (visual analog scale) pain scores of 2 treatment arms over 24 h after UFE (uterine fibroid embolization). A mixed effect model with total opioid consumption as a covariate (adjusted value) was used for comparison of the IV acetaminophen/IV ibuprofen group and the IV ketorolac group (p=0.243 for all time points)

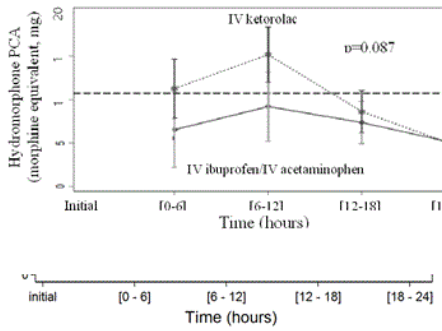

Figure 3: Difference of opioid consumption (in morphine equivalents) between IV ibuprofen/IV acetaminophen group and active comparator, IV ketorolac

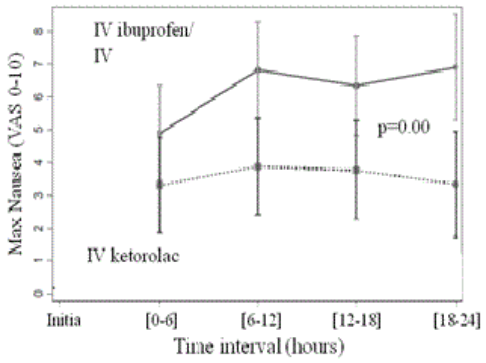

Figure 4: Mean difference in the max VAS nausea scores between IV acetaminophen/IV ibuprofen group and IV ketorolac group over 24 h with covariates at baseline

Adverse events

No serious adverse events were reported during the trial. No patient was withdrawn from the study as a result of adverse events or complications.

Discussion

We anticipated performing an interim analysis of a larger study. Due to the introduction of newly developed modalities such as radial artery entry, superior hypo gastric nerve block, intra-arterial lidocaine injection, and dexamethasone, which have demonstrated an improvement in patient satisfaction, pain control, and opioid sparing effects after UFEs, we decided to terminate the study after the interim analysis and analyse the data as if it were the final study [18-21]. Thirty-two subjects of the total 40 were the primary focus and analysis: the combined IV acetaminophen/ibuprofen group and the IV ketorolac group. As described above, subjects were randomized unevenly for the interim analysis. We hypothesized that the groups which were most likely to demonstrate a significant difference would be the acetaminophen/ibuprofen combined group and the ketorolac group. Although combined oral medications of acetaminophen and ibuprofen are available and currently in use [22], the safety of administering this combination of IV formulations of these two drugs is not well documented.

The results of this study demonstrate that the use of IV acetaminophen and IV ibuprofen alone and in combination did not produce any untoward effects. There was a trend (p=0.087) in the reduction of opioid consumption when pre-emptive IV acetaminophen and IV ibuprofen were administered compared to IV ketorolac, an active comparator. However, a decrease in pain did not reach statistical significance.

Previous studies have confirmed that IV ibuprofen and IV ketorolac improve postoperative pain and have opioid sparing effects [23,24]. IV acetaminophen demonstrates similar pain control to opioids, as well as the benefit of opioid sparing [25,26]. This is consistent with our findings. Furthermore, we are unaware of any studies comparing the efficacy and opioid sparing effects of IV acetaminophen in combination with NSAIDs. These drugs are the recommended baseline agents in multimodal postoperative pain control [27]. Therefore, it was important to compare and contrast the efficacy and outcomes of these medications singularly and in combination.

The consideration of IV vs. oral NSAID and acetaminophen formulations immediately post-procedure and for up to 24 h is recommended, as IV dosing is more reliable in the setting of nausea and vomiting, and the pharmacokinetic profiles demonstrate increased blood levels and duration of action. Additionally, the rationale of minimizing opioids by increasing the use of NSAIDs and acetaminophen in IV format provides fewer opioid-related side effects. With regard to IV acetaminophen compared to PO, there may be added benefit in lack of first pass effect, allowing for an increase in dose (4 mg vs 3.4 mg), producing increased analgesia per given dose and limiting hepatotoxicity [28].

There are several limitations in this study. The sample size of the study was intended to be larger, but an interim analysis became a final analysis with 40 subjects due to technical advancement in the care for the intended population. Therefore, we focused on the combined groups. Thus, the data of the individual ibuprofen and acetaminophen groups (4 subjects each) were excluded due to small sample size. Another potential

limitation may also be that administering IV ketorolac post-procedure (as per Package Insert) rather than pre-emptively as with the IV acetaminophen and IV ibuprofen, may have affected the outcomes.

Conclusion

In conclusion, when given in combination and pre-emptively, IV acetaminophen and IV ibuprofen demonstrated comparable pain relief but less opioid requirement compared to IV ketorolac in UFE patients. For the precise determination of opioid sparing effects of acetaminophen and ibuprofen, further study with a larger number of subjects is required, possibly with the active comparator administered pre-emptively. Surprisingly, the IV acetaminophen/IV ibuprofen group had statistically significant increased maximum nausea when compared to the active comparator control IV ketorolac, mandating adequate anti-emetic therapy with the use of all medications.

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