Routine ketorolac at oocyte retrieval decreases postoperative narcotic use by more than 50%

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Objective: To study the impact of routine ketorolac administration during oocyte retrieval on the proportion of patients who require postoperative narcotics for analgesia.
Design: Retrospective cohort study.
Setting: Single, university-affiliated infertility clinic.
Patient(s): All women undergoing oocyte retrieval between July and November 2016 (non-ketorolac group [NKG]; n = 826) and April-August 2017 (ketorolac group, KG; n = 1780).
Intervention(s): A single 30 mg intravenous dose of ketorolac was administered after the oocyte retrieval procedure.
Main outcome measure(s): The number of patients who required postoperative narcotic analgesia, postoperative complication rate, and fresh embryo transfer pregnancy outcomes were examined.
Result(s): In the KG, we found a significant decrease in the patients who required narcotics after oocyte retrieval compared with the NKG (12% KG vs. 25.5% NKG). We found no significant change in the clinical pregnancy rate (CPR) resulting from fresh embryo transfer after our intervention (NKG CPR 32.6%, KG CPR 32.4%). Furthermore, there was no increase in postoperative bleeding complications in the KG.
Conclusion(s): Routine use of ketorolac at the time of oocyte retrieval may decrease the rate of postoperative opioid use without adversely impacting pregnancy and complication rates. (Fertil Steril Rep® 2021;2:156–60. ©2021 by American Society for Reproductive Medicine.)
Key Words: IVF, ketorolac, non-narcotic analgesia, NSAID, oocyte retrieval, postoperative pain control

Opioid dependence and addiction are a growing public health crisis in the United States, exacerbated by the unnecessary or excessive administration of postoperative narcotics by health professionals (1–3). Utilization of non-narcotic analgesics in an outpatient Surgery Center setting would mitigate the need to prescribe such medication, and this approach has been shown to be efficacious. A randomized clinical trial that evaluated the treatment of patients who presented at the emergency room with acute extremity pain showed that the administration of ibuprofen and acetaminophen produced a pharmacological effect that was bioequivalent to that of oxycodone and acetaminophen in symptomatic relief (4).

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in the field of infertility and assisted reproductive technology (ART), however, is controversial. Two major concerns regarding the use of NSAIDs in patients actively undergoing infertility treatment with in vitro fertilization (IVF) are suppression of the response to the ovulatory/LH trigger and the subsequent impact on implantation after fresh embryo transfer (ET) and the possibility of increased bleeding immediately after vaginal oocyte retrieval.

NSAIDs inhibit cyclooxygenase (COX1 and COX2), leading to the inhibition of prostaglandins (5). This mechanism underlies much of the concern surrounding NSAID use in patients undergoing infertility treatment, as prostaglandins are a key regulator of many reproductive processes. Specifically, disruption of prostaglandin production can inhibit ovulation. Prior

Received April 24, 2020; revised February 2, 2021; accepted February 5, 2021.
E.A.S. has nothing to disclose. D.A.V. has nothing to disclose. A.Q.L. has nothing to disclose. D.S. has nothing to disclose. D.A.R. has nothing to disclose. A.S.P has nothing to disclose.
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Fertil Steril Rep® Vol. 2, No. 2, June 2021 2666-3341

https://doi.org/10.1016/j.xfre.2021.02.003

studies demonstrating this effect include a commonly cited case report of four women with autoimmune disease treated with high dose NSAIDs (6). These infertile women were able to conceive either spontaneously or with ART after cessation of diclofenac. Although this clinical scenario is not generalizable to most infertility patients who typically use NSAIDs, the study has influenced decision-making among infertility specialists.

Another concern related to NSAID use in IVF is its potential effect on embryo implantation. Reproductive endocrinologists have historically had reservations with the administration of an NSAID at the time of oocyte retrieval before the transfer of a fresh embryo, despite the wash-out interval period of 3–5 days between the procedures. These concerns are in contradistinction to the fact that aspirin (an NSAID) has been identified as a possible cycle modulator believed to improve implantation. The administration of low-dose aspirin (80–100 mg daily) is sometimes used as an adjunct therapy during IVF cycles to enhance implantation, presumably by positively affecting uterine blood flow and neo-vascularization (7). A recent Cochrane review concluded that, on the basis of the available data from randomized controlled trials, there is currently no evidence of the benefit of aspirin use in women undergoing IVF (8). Studies assessing the use of low-dose aspirin, as well as other NSAIDs such as indomethacin as adjunctive therapy, have shown either benefit or no difference in pregnancy outcomes (9–12). Regardless of the lack of data suggesting a negative impact on IVF success, providers are willing to use low-dose aspirin before ET, yet reticent to administer NSAIDs such as ketorolac and ibuprofen for pain control after oocyte retrieval.

A significant concern pertaining to NSAID use at the time of oocyte retrieval (as with other surgical procedures) is the possibility of an increased risk of postoperative bleeding and the associated morbidity of a clinically significant hemoperitoneum. NSAID-induced platelet dysfunction increases bleeding time, as such, NSAIDs are typically avoided in the preoperative period. Due to these concerns, the intraoperative use of intravenous NSAIDs such as ketorolac has been historically avoided, despite a lack of data supporting the risks associated with its administration during or after oocyte retrieval. Data from other surgical specialties published in a 2012 meta-analysis that reviewed 18 studies involving a total of 1,321 patients found no increase in complications, including clinically significant postoperative bleeding, between the ketorolac vs. the control group. Moreover, pain control in the KG was superior to that experienced by patients in the control group and equivalent to those who received opioids (13). Since this data was published, postoperative NSAID administration has increasingly become a common pain control modality in many surgical specialties, especially in light of the ongoing opioid epidemic.

Similar outcomes have been reported among women undergoing gynecologic procedures, and in the IVF setting there appears to be no impact on pregnancy rates related to the use of NSAIDs compared with narcotics. The objective of our study is to examine the effects of routine ketorolac use on post-oocyte retrieval pain control and pregnancy rates in subsequent fresh ET. We hypothesized that the use of routine ketorolac would improve pain relief and decrease postoperative narcotic use, without an adverse impact on fresh ET clinical pregnancy rates (CPR) or incidence of postoperative complications.

MATERIALS & METHODS

Patients

A retrospective cohort study was performed at a single, large university-affiliated infertility center. All patients undergoing oocyte retrieval between July 22 to November 1, 2016 (non-ketorolac group [NKG]) and April 13 to August 28, 2017 (ketorolac group [KG]) were evaluated. The primary outcome was the number of patients who required postoperative narcotics in the post-anesthesia care unit (PACU). The rates of postoperative complications related to bleeding or pain such as diagnostic laparoscopy, blood transfusion, and/or hospitalization, as well as fresh ET pregnancy outcomes, including positive pregnancy test, CPR, miscarriage rate, and live birth rate were also compared. We defined a clinical pregnancy as the presence of an embryo with cardiac activity on first-trimester ultrasound. The CPR in our analysis, therefore, was the number of viable clinical pregnancies per ET.

Analgesic Protocols

At the start of the oocyte retrieval procedure, nearly all patients receive 100 mcg of fentanyl via intravenous (IV) administration by an anesthesia physician. In December 2016 our center added a single 30 mg IV dose of ketorolac given after the oocyte retrieval procedure before exiting the operating room. Before this time, IV narcotics (including more fentanyl, as well as other IV and oral narcotics) were given on a case-by-case basis postoperatively. By April 2017, all patients routinely received IV ketorolac at egg retrieval, except those with a contraindication such as a known bleeding disorder, severe allergy, renal dysfunction with abnormal baseline creatinine, or concern for ongoing intraoperative bleeding (fewer than 1% of patients). Fentanyl and ketorolac are now routinely given at nearly every egg retrieval procedure at our center and form the mainstay of analgesia for this category of patients. Our postoperative pain management protocol allows for the administration of narcotic pain medications based on patient symptoms and we do not administer them routinely. The PACU nurse assesses the patient's level of pain control and can administer additional narcotics if needed. A physician is always available to evaluate a patient with intractable pain.

Statistical Analysis

A four-month study period was chosen before and after the intervention to obtain a sample of convenience. A post hoc power analysis was performed at 80% power (α level of .05) that confirmed an adequate sample size. Based on the number of patients analyzed, the present study is powered to detect a 5% difference in the proportion of patients receiving postoperative narcotics, at 80% power (α level of .05). A

TABLE 1

Selected demographics of all patients undergoing egg retrievals in the non-ketorolac and ketorolac groups.

Patient demographics	Non-ketorolac group (n = 826)	Ketorolac group (n = 1780)
Average age (y), mean (SD)	36.4 (4.2)	36.0 (4.9)
Average BMI (kg/m^2), mean (SD)	26.7 (6.4)	26.7 (6.6)
Prior Gravidity of ≥1, n (%)	403 (48.8)	860 (48.3)
Prior Parity of ≥1, n (%)	212 (25.7)	463 (26.0)
Prior Spontaneous abortion, n (%)	463 (26.0)	429 (24.1)
Average AMH, mean (SD, ng/mL)	2.6 (2.4)	2.7 (3.4)
Average Day 3 FSH, mean (SD, mIU/mL)	8.9 (4.6)	8.4 (3.8)
Patients with no prior IVF cycles, n (%)	409 (49.5)	945 (53.1)
Patients with ≥1 prior IVF cycles, n (%)	417 (50.5)	835 (46.9)
Peak E2 level in IVF cycle, mean (SD, pg/mL)	2135.36 (528.8)	2250.60 (469.7)
Average No. of eggs retrieved, mean (SD)	11.32 (8.1)	11.96 (8.1)
% ICSI of all retrievals, n (%)	363 (43.9)	801 (45.0)
% PGT of all retrievals, n (%)	181 (21.9)	486 (27.3)

Note: All the P values were non-significant when the two groups were compared. BMI = body mass index; AMH = antimüllerian hormone; FSH = follicle stimulating hormone; IVF = in vitro fertilization; E2 = estradiol.

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chi-square test was performed to compare the proportion of patients requiring postoperative narcotics for analgesia, CPR, and complications between the two groups with $P<.05$ considered statistically significant.

The study was approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigation (Protocol No.: 2018P000790).

RESULTS

A total of 826 patients underwent vaginal oocyte retrieval during the study period before the commencement of routine ketorolac usage. These patients received fentanyl only for intraoperative pain control (NKG). In the KG, 1780 patients received a single dose of 30 mg IV ketorolac at the time of egg retrieval during the study period after routine ketorolac use was instituted. The few patients who did not receive ketorolac had contraindications to its use.

The baseline demographics and oocyte yield of the NKG vs. the KG were similar (Table 1). The two groups were similar with regard to age, body mass index, ovarian reserve testing, gravidity and parity, response to ovarian stimulation, and other baseline factors. In addition, the two groups did not differ in terms of infertility diagnoses when comparing ovulation disorders, male factor, tubal factor, and unexplained infertility. In the KG, we found a significant decrease in the proportion of patients requiring postoperative narcotics after oocyte retrieval vs. NKG (12.0% vs. 25.5%, $P<.0001$). Nearly half of all patients (45.7% in the NKG and 46.7% in the KG) had a fresh ET. We found no significant differences in the CPR between the NKG vs. the KG (32.6% vs. 32.4%, $P=.95$), after fresh ET (Table 2).

Postoperative complications were rare in both groups. The rate of hospitalization and/or surgery related to postoperative bleeding complications, including pain from hemoperitoneum or need for re-operation because of ongoing bleeding, was less than 1% in both groups. Although the rate was low in each group, the incidence of significant complications was lower in the KG (0.7% NKG vs. 0.06% KG, $P=.003$). In the NKG, five patients had bleeding complications and re-presented with pain and signs/symptoms of intraabdominal bleeding. Of the five patients, four were managed surgically with urgent diagnostic laparoscopy and evacuation of the hemoperitoneum, one of which underwent unilateral oophorectomy for uncontrolled bleeding from the ovary. The fifth patient was managed medically with the transfusion of two units of packed red blood cells. In the KG, there was one postoperative complication, due to intraperitoneal bleeding. This patient was managed surgically with diagnostic laparoscopy and evacuation of the hemoperitoneum, with no ongoing bleeding observed at the time of her surgery.

Both groups also had similar cycle characteristics and pregnancy outcomes. Specifically, the proportion of patients who had a cleavage stage (day 3) or blastocyst stage (day 5) ET was similar to those who had a fresh transfer. However, there were a small number of patients who underwent fresh ET and preimplantation genetic testing (PGT) in both groups with the PGT cycles being done with a "freeze all" approach. There were fewer patients in the KG (4.9% in the KG vs. 8.2% in the NKG) who had a fresh ET with PGT.

DISCUSSION

In our study, the routine use of an intravenous NSAID safely decreased the proportion of patients requiring postoperative narcotics for analgesia by over 50% without impacting the fresh ET pregnancy rate. There was no increase in the rate of complications, including postoperative bleeding, following ketorolac use.

Data pertaining to NSAID use in the field of ART is limited, but our study adds to the existing literature supporting its efficacy and safety in the post-surgical setting. Mesen et al. (14) retrospectively reviewed 454 patients and found no apparent deleterious effects on IVF pregnancy outcomes when ketorolac was given after oocyte retrieval. Pain scores were better in the KG compared with the control group. Postoperative bleeding or other complications were

TABLE 2

Narcotic use and complications in the non-ketorolac and ketorolac groups for all egg retrievals as number of patients (%); cycle characteristics and pregnancy outcomes as number of patients (%) for fresh autologous transfers.

	Non-ketorolac group (n = 826)	Ketorolac group (n = 1780)	*P* values
Per Egg Retrieval			
Patients receiving any post-op narcotics	211 (25.5)	214 (12)	<.001
Complications (patients requiring hospitalization and/or re-operation)	5 (0.006)	1 (0.0006)	NS
No. of Fresh ET (% per Retrieval)	378 (45.7)	832 (46.7)	NS
Per Fresh ET			
Cleavage stage ET	135 (35.7)	265 (31.9)	NS
Blastocyst stage ET	243 (64.3)	567 (68.1)	NS
% ICSI of fresh ET	166 (43.0)	363 (43.6)	NS
% PGT of fresh ET	31 (8.2)	41 (4.9)	<.05
Positive pregnancy test	174 (46.1)	384 (46.2)	NS
CPR of fresh ET	123 (32.6)	270 (32.4)	NS[a]
Miscarriage rate[b]	18 (4.8)	58 (7.0)	NS
Live birth rate	109 (28.8)	219 (26.3)	NS

Note: Data presented as n (%), unless noted otherwise. CPR = clinical pregnancy rate (i.e. presence of embryonic parts with cardiac activity on ultrasound); ET = embryo transfer; ICSI = intracytoplasmic sperm injection; PGT = preimplantation genetic testing.
NS signifies non-significant difference (P>.05).
[a] *P*= .95
[b] Calculated from patients with a loss after an ultrasound-confirmed pregnancy.

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not evaluated between the groups. Our study is the first to evaluate these parameters and many others, including live birth rate on a larger scale, in nearly 2,500 patients.

We found that both groups were generally similar in cycle characteristics and pregnancy outcomes except the rate of PGT in fresh ET, which was lower in the KG. We believe this is because of a natural evolution in practice, more recently favoring no fresh ET when PGT-A is utilized. We also believe this trend to be unrelated to the use of ketorolac at egg retrieval and unlikely to skew our data due to small numbers in both groups. However, it is necessary to report this. Importantly, we reported pregnancy outcomes data through live birth rate, in the case of any possible underlying effects of ketorolac on placentation that could affect subsequent obstetric outcomes.

There are some possible limitations to our study. Given its retrospective nature, there may be confounding factors that would influence outcomes between the KG and NKG. For example, we were unable to obtain information on the duration of the oocyte retrieval procedure, baseline and postoperative pain scores, and history of pain syndromes, factors that can affect a patient's perception and need for postoperative narcotics. In addition, other details related to the anesthesia record, such as the total dose of narcotics given, and the exact number of patients from whom ketorolac was withheld, were not obtained. Our center's Anesthesia Director estimates that <1% of patients are ineligible to receive ketorolac, due to a severe NSAID allergy or other contraindication, therefore, we believe this would be unlikely to meaningfully skew our data. Although these additional parameters may add to the analysis, the finding that any use of narcotics at all was decreased with the addition of ketorolac is clinically significant and unlikely to be explained by other confounders. A well-designed prospective randomized controlled trial would mitigate these latent confounders.

The strengths of our study include its large sample size of patients undergoing treatment in an ART insurance-mandated state, enhancing the diversity of the patient population. The evaluation of postoperative complications provides reassurance that providers can safely administer ketorolac intraoperatively, although the low prevalence of complications in both groups did not provide enough power to detect a statistical significance. The benefits of NSAIDs over narcotics include enhanced patient satisfaction resulting from improved pain control (15–17). Furthermore, the cost of ketorolac per 30 mg dose is similar to fentanyl per 100 mcg dose ($2.92 vs. $2.76), and given there was an overall reduction in postoperative narcotic administration, this represents a cost-effective change.

CONCLUSION

Pain control is an important aspect of procedural medicine but must be balanced with patient safety at the individual and societal levels. Alternatives to narcotic medication are available and should be utilized. Some studies have shown that non-narcotic pain medication can be as effective as narcotics, without the potentially dangerous side effects, ranging from severe constipation to increased tolerance with subsequent risk of dependence and overdose.

This study provides some evidence in support of the routine use of ketorolac at the time of egg retrieval. There does not appear to be any compromise with respect to the goal of IVF while improving patient satisfaction and decreasing exposure to opioids. This simple intervention does not appear to change the fresh ET pregnancy rate but does significantly decrease PACU narcotic administration with fewer narcotic prescriptions written at discharge. In light of the known problems associated with opioid overuse and addiction, clinicians should choose non-narcotic analgesics whenever possible.

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