Oral Ketorolac for Pain Relief During Intrauterine Device Insertion: A Double-Blinded Randomized Controlled Trial

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Abstract

Objective: To evaluate if oral ketorolac provides effective pain relief during placement of an IUD for contraception.

Methods: We conducted a double-blinded randomized controlled trial in a community hospital in Columbus, Ohio. Participants that met eligibility criteria were consented and randomized to receive either oral ketorolac 20 mg or placebo 40 to 60 minutes before IUD placement. Both participants and providers were blinded to the randomization group. The primary outcome was pain reduction (measured on a 0−10 numerical rating scale) during IUD placement. Data was analyzed using a two-sided independent samples *t*-test. An a priori sample size was calculated to detect a clinically meaningful difference of 2 points with 80% power. The type I error probability was $\alpha = 0.05$.

Results: Seventy-two participants were enrolled and randomized between May 2014 until March 2016. Thirty-five in the ketorolac group and 36 in the placebo group were analyzed. There were no differences in baseline characteristics between participants or providers, as well as pain ratings prior to the procedure, at tenaculum placement, or at uterine sounding. There was a significant decrease in the pain of the ketorolac versus the placebo group rating at IUD deployment (4.2 vs. 5.7, $P = 0.031$), overall pain rating (3.6 vs. 4.9, $P = 0.047$), and pain 10 minutes after the procedure (1.1 vs, 2.5, $P = 0.007$).

Conclusion: Oral ketorolac given 40 to 60 minutes prior to IUD insertion is effective in reducing pain during IUD deployment, overall pain, and pain 10 minutes after IUD placement.

Résumé

Objectif : Déterminer si le kétorolac administré par voie orale soulage efficacement la douleur pendant l'insertion d'un DIU aux fins de contraception.

Méthodologie : Nous avons mené un essai clinique randomisé à double insu dans un hôpital communautaire de Colombus, en Ohio. Les participantes répondant aux critères d'admissibilité et ayant donné leur consentement ont aléatoirement reçu un placebo ou 20 mg de kétorolac administré par voie orale de 40 à 60 minutes avant l'insertion d'un DIU. La répartition aléatoire a été faite à l'insu des participantes et des fournisseurs de soins. Le critère d'évaluation principal était le soulagement de la douleur (mesurée sur une échelle numérique de 0 à 10) durant l'insertion du DIU. Les données ont été analysées au moyen d'un test t à deux échantillons indépendants. La taille de l'échantillon a été calculée a priori pour obtenir une différence cliniquement significative de deux points et une puissance de 80 %. La probabilité d'erreur de type I était $\alpha = 0,05$.

Résultats : Au total, 72 participantes ont été recrutées et aléatoirement réparties entre mai 2014 et mars 2016. Respectivement, 35 et 36 patientes se sont retrouvées dans le groupe kétorolac et dans le groupe placebo. Aucune différence n'a été observée dans les caractéristiques de référence des patientes et des fournisseurs de soins, ni dans l'évaluation de la douleur avant l'intervention, à l'installation du tenaculum et pendant le sondage utérin. Les patientes du groupe kétorolac, comparativement à celles du groupe placebo, ont signalé une douleur significativement moins intense à l'insertion du DIU (4,2 c. 5,7; $P = 0,031$), de la douleur globale (3,6 c. 4,9; $P = 0,047$) et de la douleur ressentie 10 minutes après l'intervention (1,1 c. 2,5; $P = 0,007$).

Conclusion : La prise de kétorolac par voie orale de 40 à 60 minutes avant l'installation d'un DIU réduit efficacement la douleur durant l'insertion, la douleur globale et la douleur ressentie 10 minutes après l'intervention.

Key Words: Anti-inflammatory agents, non-steroidal analgesics, non-narcotic analgesics, IUD, contraception

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INTRODUCTION

In the United States, 11.6%, or 4.4 million women report using an IUD for contraception.[1] With typical use, unintended pregnancy rates in the first year of IUD contraception are 0.8% (Copper T)[2] and 0.2% levonorgestrel.[3−5] Long-acting, reversible contraception methods help reduce the long-term cost of unintended pregnancies, especially among women of colour and those

with lower education and socioeconomic status who are at much greater risk of unplanned pregnancy.[6]

A common deterrent to intrauterine contraception is the fear of pain during placement.[7–9] Methods of pain relief during IUD insertion must be fast-acting but have minimal sedation. There have been many attempts to find effective pain relief during IUD placement; however, neither ibuprofen or naproxen were satisfactorily effective.[7,10–12] Self-administered lidocaine gel has been demonstrated to decrease pain with tenaculum placement, but not overall IUD insertion.[13] Misoprostol has been used to increase cervical ripening; however, pain was not decreased, and side-effects of nausea and vomiting have been reported.[14–16]

Ketorolac, a non-steroidal anti-inflammatory drug, works by reversibly inhibiting cyclooxygenase-1 and 2.[17] Time to peak plasma concentration ketorolac in the oral form is 44 minutes,[17] and previous studies have found one dose of ketorolac can be as potent as morphine.[18] Ketorolac has been well-established for pain control in the immediate post-operative period.[19] A recent study showed that intramuscular ketorolac was effective in reducing pain after IUD insertion, but 20% of the participants reported that after the procedure, the injection site was as painful as the IUD placement.[20] The current study was designed to evaluate if there is reduced pain during IUD placement using oral ketorolac 40 to 60 minutes before the procedure compared to a placebo.

METHODS

This randomized controlled trial was conducted at OhioHealth Riverside Methodist Hospital in Columbus, Ohio. Approval was obtained through our institutional review board IRB#: OH1-13-00503 and registered at clinicaltrials.gov ID: NCT03031795. Eligibility criteria included non-pregnant, English-speaking women who were 18 years of age or older desiring an IUD (either intrauterine copper contraception [T380A] or levonorgestrel-releasing intrauterine system [52mg]) for contraception. Exclusion criteria included: enrollment in another study, premedication with any type of analgesic medication, daily narcotic pain use, contraindication to an IUD including positive cultures for gonorrhea or chlamydia, and contraindications to ketorolac including weight under 50 kg, allergy to NSAIDS, medical history of liver disease, renal disease, peptic ulcer disease, or recent gastrointestinal bleed.

Patients were recruited from both the community medicine clinic and a private practice office. Following obtainment of informed consent, baseline participant characteristics were collected by a research coordinator. No stipend was provided to participants.

As part of the enrollment process, the daily/weekly schedule was screened for appointments involving (or possibly involving) an IUD placement. When possible, the study research coordinator attempted to contact the patient prior to the IUD placement appointment. Since the study required the patient to take the study medication 40 to 60 minutes prior to placement and have not taken any other premedications, being able to schedule this extra time beforehand was beneficial. However, we found patients oftentimes did not return the coordinator's calls.

Thus, the study research coordinator would approach the patient and present the study at the time of their visit. If the patient was interested, they were then consented and given the study medication. In these situations, this delayed the appointment time created recruitment challenges, as patients did not have the additional time to spare or they had taken excluded medications prior to the visit.

In order to increase enrollment, the private office was added as a recruitment site via IRB amendment in October 2014. Patients were also called ahead of time and presented a description of the study. If they were agreeable, they planned to arrive early so as not to delay the clinic schedule. This population was more reliable, but there were still patients that did not show for their appointments.

Our institution's investigational pharmacy prepared packets of placebo or ketorolac 20 mg in a 1:1 ratio based on a randomization list created at randomization.com by the biostatistician (JOE), which were labeled sequentially by our investigational pharmacy. To assure a double-blinded study, every packet contained two red capsules and only the pharmacy was aware of the randomization allocation. Packets were assigned in sequential order. After a participant met eligibility criteria and consent was obtained, the study medication was provided. The research coordinator or physician who obtained consent observed the participant swallowing the capsules.

The time the study medication was taken was recorded and the procedure started 40 to 60 minutes later. The primary outcome was pain during various points of the procedure and

ABBREVIATIONS

IRB	institutional review board
LNG	levonorgestrel
LNG-IUS	levonorgestrel-releasing intrauterine system
NSAID	non-steroidal anti-inflammatory drug