

Original Article

Comparison of the Effects of Meloxicam and Dexketoprofen on Postoperative Adhesion Formation in a Rat Uterine Horn Surgical Model

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ABSTRACT **Study Objective:** To compare the effects of 2 nonsteroidal antiinflammatory drugs of different chemical classes (meloxicam and dexketoprofen) on postoperative intraabdominal adhesion formation in a rat model.

Design: Experimental study (Canadian Task Force classification I).

Setting: Center for research and development.

Animals: Thirty female Wistar albino rats.

Interventions: The animals were randomly assigned to 1 of 3 groups (10 rats per group) and received intramuscular injections of 0.5 mg/kg dexketoprofen (group 1), 0.5 mg/kg meloxicam (group 2), or 1 mL sterile saline solution (control; group 3) daily for 2 days. Laparotomy was performed, and 1 of the uterine horns was damaged via monopolar electrocautery, whereas an incision was made in the other horn using a scalpel and was sutured to promote adhesion formation. The surgeons were blinded to the treatment method. Drug administration was continued for 5 days. The animals were euthanized at 14 days after surgery.

Measurements and Main Results: Intraperitoneal macroscopic and microscopic adhesions were assessed using standard adhesion scoring systems. Macroscopic adhesion scores were similar among the 3 groups in each horn ($p > .50$). The total histologic score was significantly lower in the meloxicam group than in the control group (8.0 vs 15.5; $p = .006$). Dexketoprofen did not significantly affect the total histologic score (11.0 vs 15.5; $p = .09$) or individual items (i.e., inflammation, fibroblastic activity, foreign body reaction, collagen formation, and vascular proliferation) compared with the control group ($p > .02$). Meloxicam significantly inhibited inflammation and collagen formation compared with the control group ($p < .02$). Meloxicam was also significantly superior to dexketoprofen in reducing inflammation ($p = .006$).

Conclusion: Although meloxicam did not affect clinical adhesion formation, it significantly decreased histologic scores compared with those of the control group. Therefore, meloxicam may be suitable in reducing postoperative intraabdominal adhesion formation. Journal of Minimally Invasive Gynecology (2013) 20, 185–191 © 2013 AAGL. All rights reserved.

Keywords: Adhesion formation; Dexketoprofen; Meloxicam; Nonsteroidal antiinflammatory drugs; Rat

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Adhesions are abnormal fibrous connections that may contain vascular channels and that join tissue surfaces at abnormal locations [1]. Postoperative adhesions develop in as

many as 50% to 97% of patients after abdominal surgery [2,3] and frequently cause postoperative life-threatening ileus, chronic abdominopelvic pain, and infertility. They

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may also result in longer operation times and increase the risk of intraoperative complications [4].

Several nonsteroidal antiinflammatory drugs (NSAIDs) have been used in many animal and clinical trials to minimize or prevent adhesion formation after surgery [5–8]. Substances used in an attempt to prevent adhesions must inhibit adhesion formation without compromising wound healing, even in the presence of blood or other body fluids. They must also have antiinflammatory properties, lack immunogenic determinants, be biodegradable, remain *in situ* after application, be easy to handle, be inexpensive, and have an immediate effect [9]. NSAIDs may be able to prevent or reduce the initial inflammatory stage of adhesion formation by inhibiting prostaglandin production [5–7,10]. However, these agents have not been sufficient to warrant their routine use during pelvic surgery.

Meloxicam is an NSAID that preferentially inhibits cyclooxygenase (COX)–2 rather than COX-1. COX-2 is induced by inflammatory stimuli in pathophysiologic conditions [11]. Dexketoprofen trometamol, another NSAID, is a water-soluble salt of the dextrorotatory enantiomer of ketoprofen. Dexketoprofen is often used as an analgesic and an antiinflammatory agent and is one of the most potent *in vitro* inhibitors of prostaglandin synthesis [12]. Meloxicam and dexketoprofen are NSAIDs characterized by long half-life, low risk of adverse effects, and good antiinflammatory and analgesic effects, and they can be used for a prolonged period. Consequently, both drugs are widely used for postoperative pain relief.

The objective of the present study was to compare the effects of meloxicam and dexketoprofen, 2 NSAIDs of different chemical classes, on prevention of postsurgical intraabdominal adhesions via their antiinflammatory properties.

Materials and Methods

The experimental research protocol was approved by the Animal Research Ethics Review Committee at Ankara Gulhane Military Medical Academy, where the study was performed. The international guidelines of the Association for Assessment and Accreditation of Laboratory Animal Care were followed when designing and conducting the study.

Thirty sexually mature, nonpregnant, female Wistar albino rats (weight, 180–230 g) were individually caged under conditions of constant temperature (21°C–22°C) and humidity (40%–50%), with a 12-hour dark/light cycle. The rats were provided free access to water and standard rodent chow. The animals were randomly divided into 3 groups (10 rats per group). The randomization sequence used was produced by a computerized random-number generator. Group 1 received 0.5 mg/kg/d dexketoprofen (Arvels injection, 50 mg/2 mL; Menarini International, Florence, Italy) [13], group 2 received 0.5 mg/kg/d meloxicam (Melox injection, 15 mg/1.5 mL; Nobel İlaç San ve Tic AS, Istanbul,

Turkey) [14], and group 3 (control) received sterile saline solution. The drugs or saline solution were injected intramuscularly into the gluteal region.

Two days after the first injection, the rats were anesthetized via intraperitoneal injection of 75 mg/kg ketamine hydrochloride and 10 mg/kg xylazine hydrochloride. The abdominal skin was shaved, and 10% povidone iodine solution was applied for antiseptis. Sterile, powder-free, latex gloves were used during all surgical procedures. Researchers (H.L.K. and S.M.A.), who were blinded to the experimental group, made a midline incision approximately 3 cm long to expose the uterine horns. Monopolar electrocautery (50 W) was used to create a 1-cm lesion on the antimesosalpingeal side of the right proximal horn. The cauterization lasted 3 to 5 seconds. A 1-cm incision was made in the same region of the left horn using a No. 15 scalpel and was sutured using 3-0 polyglactin 910. Blood and fibrin material were removed from the surgical site after confirming that hemostasis had been achieved, and the abdominal wall was closed in a single layer using 2/0 non-polyglactin 910 suture.

The NSAIDs or saline solution were administered for 5 days after surgery, for a total of 7 days of administration. No antibiotic agents were administered during the entire procedure.

The study end points were macroscopic and histologic adhesion scores, which were determined on day 14. All 30 rats were euthanized at 14 days after surgery. A repeat laparotomy was performed with an inverse U-shaped incision that was centered over the original midline incision. The intraperitoneal macroscopic adhesions were identified, and an established adhesion scoring system [15,16] was used by the same researchers blinded to the treatment received. Two researchers (H.L.K. and S.M.A.) evaluated and determined the macroscopic adhesion score together. Adhesion extent and tenacity were also evaluated. The extent of adhesion was defined as the percentage of the injured area that was covered by adhesive tissue and was graded as follows: 0% = 0, <25% = 1, 25%–50% = 2, and >50% = 3. Lesion tenacity was graded as showing no resistance to separation (score = 0), moderate force required for separation (score = 0.5), or sharp dissection necessary for separation (score = 1) (Fig. 1).

The cumulative adhesion score for 1 horn per rat was calculated as the sum of the scores for adhesion extent and tenacity. The median score was used as the final score for each horn. After completing macroscopic scoring, the previously sutured region of the left horn was excised (approximately 1 cm long). Tissue sections were prepared and stained with hematoxylin-eosin and Masson trichrome stains. A pathologist (H.K.) blinded to the treatment groups evaluated the specimens under a light microscope and scored them according to 5 characteristics: inflammation, fibroblastic activity, foreign body reaction, collagen formation, and vascular proliferation (Table 1). The total histologic score was calculated as the sum of the scores for the 5 individual features (Fig. 2) [17].

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