ORIGINAL ARTICLE

Assessing the Effects of Lornoxicam and Dexketoprofen on Mouse Fibroblast Cells

Lornoxicam ve Dexketoprofen'in Fare Fibroblast Hücreleri Üzerindeki Etkilerinin Değerlendirilmesi

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Abstract

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis, are used in many clinical areas. Although they are advantageous because of their analgesic, anti-inflammatory, and antipyretic properties, their effects on tissue healing are controversial. Dexketoprofen and lornoxicam are widely used, new-generation NSAIDs. However, their effects on fibroblasts, which are important for healing, are unknown. Herein, we aimed to investigate the effects of these two drugs on fibroblast viability, migration, and collagen expression.

Methods: L929 mouse fibroblasts were cultured *in vitro*. Viability assays, wound-healing assays, and gene expression analyses were performed after 24 hours of treatment with lornoxicam and dexketoprofen at a 0–1-mM dosage. The viability test, wound-healing test, and gene expression analysis were performed using the MTT method, by calculating the closed area, and by qRT–PCR, respectively.

Results: Lornoxicam and dexketoprofen at doses of 0–1 mM dose-dependently decreased viability, and changes in cell morphology were observed. Lornoxicam 1 µM and dexketoprofen 10 µM doses significantly reduced the migration rate of L929 cells compared with the control group (****p<0.0001). After 24 hours, COL1A1 expression in L929 cells was 0.027 and 0.015 when 1 and 10 µM of lornoxicam and dexketoprofen were applied.

Discussion and Conclusion: Lornoxicam and dexketoprofen have negative effects on the viability, migration, and type 1 collagen synthesis of fibroblasts. Considering these negative effects on fibroblasts is crucial while using these drugs.

Keywords: Dexketoprofen; Fibroblast; Lornoxicam; NSAID

L ornoxicam is a nonsteroidal anti-inflammatory drugs (NSAIDs) used to treat musculoskeletal and joint disorders, such as osteoarthritis and rheumatoid arthritis. [1] It exerts its anti-inflammatory effects by acting on the synthesis of arachidonic acid and prostaglandin through the inhibition of cyclooxygenase enzymes.[2] NSAIDs exhibit differences in COX isoenzyme inhibition and are classified as "conventional" or "nonselective," acting as COX-

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1 and COX-2 inhibitors.[3] Similarly, dexketoprofen is used as an analgesic and NSAID and is one of the most potent *in vitro* inhibitors of prostaglandin synthesis. Dexketoprofen was designed to reduce the duration of action, improve potency, and lessen the gastrointestinal side effects.[4] Several NSAIDs can cause gastrointestinal, liver, bone marrow, and renal toxicities, leading to gastrointestinal bleeding, ulceration, fulminant liver failure, and acute tubular necrosis. Compared with other NSAIDs, lornoxicam prevents gastrointestinal side effects.[5] The side effects of dexketoprofen can be observed in the gastrointestinal tract, central nervous system, circulatory system, liver, kidneys, respiratory system, ears, systemic reactions, platelet count and function, and skin.[6] Dexketoprofen and lornoxicam are NSAIDs with analgesic, antipyretic, and anti-inflammatory properties and common side effects.

NSAIDs are inexpensive and effective drugs that are widely used to treat pain, edema, and heterotopic ossification associated with trauma or degenerative changes.[7] NSAIDs can be prescribed after soft tissue injury or surgery to help manage pain and reduce inflammation; however, their use is controversial because of their adverse effects on wound healing.[8] Although NSAIDs usually have negative effects on mesenchymal tissue healing, their effects on fracture healing may be different.[7] A systematic review of the use of NSAIDs after knee surgery indicated that the administration of selective and nonselective COX-2 inhibitors may impair soft tissue, bone, and tendon-bone healing. However, more clinical studies are needed to better characterize the dose- and time-dependent risks of NSAIDs.[9] Similarly, a meta-analysis investigating the effects of NSAIDs after arthroscopic rotator cuff repair suggested that NSAIDs do not affect the rate of healing but considerably improve postoperative pain and functional outcomes.[10] A study evaluating the effects of NSAIDs on the proliferation of nasal polyp fibroblasts reported that budesonide and rofecoxib inhibited proliferation. This was associated with the involvement of inflammatory mediators.[11] The nonselective NSAID Naproxen regulates collagen expression and MAPK signaling.[12]

Reportedly, short-term, low-dose NSAIDs and COX-2 inhibitors did not have a detrimental effect after soft tissue injury but appeared to inhibit bone healing. Clinically, anti-inflammatory drugs should be used cautiously after sports medicine injuries and surgeries and should not be used unless bone healing is required.[13] Most studies have shown that COX-2 selective inhibitors have a negative effect on soft tissue healing, whereas nonselective COX inhibitors have no negative effect on the healing of the labrum, tendons, and ligaments. *In vitro* studies have reported that NSAIDs have a detrimental effect on the biological processes involved in tendon healing and regeneration (tenocyte proliferation, collagen, and glycosaminoglycan synthesis).[14]

In literature, NSAIDs affect tissue healing differently, based on their selectivity. Fibroblasts are important regulators in tissue healing and contribute to proliferating, migrating, and synthesizing collagen.[15] Herein, we aimed to elucidate the effects of lornoxicam and dexketoprofen, two nonselective and commonly used NSAIDs, on wound healing. The effects of lornoxicam and dexketoprofen on the viability, migration, and collagen synthesis of mouse fibroblasts were investigated. In addition to the beneficial anti-inflammatory effects of NSAIDs, clarifying the negative effects of NSAIDs on wound healing will help review their use.

Materials and Methods

This *in vitro* experimental study was conducted in 2024 at the Molecular Biology and Cell Culture Laboratory of Lokman Hekim University. In this study, cell culture, viability analysis, calcein staining, and gene expression analysis were performed.

Cell Culture

L929 (ATCC, Manassas, VA,. USA) cells were grown in DMEM (Capricorn, Germany), 10% FBS (Capricorn, Germany), 1% penicillin/streptomycin (BIOIND, Israel), and 2 mM L-glutamine (Capricorn, Germany) in complete media. The culture was maintained at 37°C, 5% CO_2, and 100% humidity. The medium was replaced every 2–3 days until the culture reached 70%–80% confluence.

Cell Viability Assay and Calcein Staining

Lornoxicam (Cas no: 70374-39-9, Sigma) and dexketoprofen tromethamine (Cas no: 156604-79-4, Sigma) were purchased for the experiments. The effects of lornoxicam and dexketoprofen on L929 viability were assessed using a spectrophotometer with the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay. For each experimental group, 5,000 cells were seeded in 96-well plates. Then, the plates were incubated at 37°C in an atmosphere of 5% CO_2. After 24 hours of incubation, dexketoprophen (0–1 µM-10 µM-50 µM-100 µM-200 µM-500 µM-1,000 µM) and lornoxicam: (0–1 µM-10 µM- 50 µM-100 µM-200 µM-500 µM-1,000 µM) drugs were treated at the respective concentrations. After 24 hours of treatment, 10 µL of MTT solution was added to each well,

with a final concentration of 0.5 mg/mL (Biotium, California, USA). For MTT analysis, the plates were incubated in the dark for 4 hours at 37℃. After the incubation period, the formed formazan crystals were dissolved by adding 100 μL dimethyl sulfoxide (DMSO) to each well. Next, the absorbance of the dissolved formazan solution was measured at a wavelength of 570 nm using a microplate reader (BioTek Synergy H1, BioTek Instruments, Winooski, VT, USA). The nontreated cell viability was accepted as 100%. This measurement enabled the assessment of cell viability and the effects of lornoxicam and dexketoprofen on the metabolic activity of L929 cells. Calcein staining was performed to observe the morphology of lornoxicam and dexketoprophen in L929 cells. A total of 5,000 cells were seeded in 96-well plates. After cell attachment, 1 μM lornoxicam and 10 μM dexketoprofen were added and allowed to adhere for 24 hours. For calcein staining, 1 μM calcein-acetoxymethyl ester (Santa Cruz Biotechnology, Inc., Dallas, TX, USA) dye was added and incubated at 37℃ in the dark for 30 minutes. A Leica DM IL fluorescence inverted microscope (Leica, Germany) was used to visualize live cells.

Wound-Healing Assay

Migration analysis was conducted via calcein staining to observe the effects of lornoxicam and dexketoprofen on the migration of L929 cells. In total, 100,000 cells were seeded in 24-well plates. When the cells reached 90% confluence in a 24-well plate, the well bottoms were scratched with a pipette tip and 1 μM lornoxicam and 10 μM dexketoprofen were applied. For each experimental group, three wells were used. Images were taken at 0 and 24 hours on a Leica DM IL microscope (Leica, Wetzlar, Germany). The cell-free area was then calculated for each group using ImageJ and converted to percentages. Lateral motility was expressed as the percentage reduction in the enclosed area at the wound sites compared with the control cells.

Gene Expression Analysis

To determine the COL1A1 expression level; L929 cells were seeded on 6-well microplates for gene expression analysis at a ratio of 105 cells. Gene expression analyses were performed at 24 hours. Dexketoprophen and lornoxicam were applied at 10 μM and 1 μM, respectively. Total RNA was isolated using Bluezol (SERVA, Germany) per the manufacturer's protocol. To evaluate COL1A1 gene expression, timed PCR was performed using the Lightcycler® 96 system (Roche Diagnostic Systems, Indianapolis, IN) and A.B.T.™ 2X qPCR SYBR-Green Master Mix (ATLAS Biotechnology, Turkey). For each PCR reaction,

10 μL of master mix, 2 μL of RNA (1μL: 20 ng/mL), 0.5 μL of forward primer (10 μM), 0.5 μL of reverse primer (10 μM), and 3 μL of H_2O were used. The primers were used at a final concentration of 10 μM. The primer sequences were as follows; COL1A1 (F: TGACTGGAAGAGCGGAGAGAGT-R: GTTCGGGCTGATGTACCAGT) and GAPDH (F: CTGCCCAGAACATCATCCCT-R:GTCCTCAGTGTAGCCCAAGA). To standardize the data, the threshold cycle (Ct) value of the GAPDH gene was used and the samples in triplicate.

Statistical Analysis

Data are presented as mean ± SD. Graphs were generated using GraphPad Prism 8.1 (GraphPad Software, San Diego, CA, USA). Statistical analysis was performed using one-way ANOVA for viability analysis using GraphPad Prism 8.1. Subsequently, a Bonferroni post-hoc test was conducted to compare the differences between the groups. Cells without any treatment were selected as control groups. A significance level of $p < 0.05$ was considered statistically significant and was indicated with an asterisk (*). The significance level was further elaborated in the analyses using the following symbols: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$.

Results

Lornoxicam and Dexketoprofen Affect the Viability of L929 Cells in a Dose-Dependent Manner

Herein, the analyses were conducted to evaluate the effects of lornoxicam and dexketoprofen on the viability and morphology of fibroblasts over 24 hours. In the lornoxicam-treated groups, a 14.5% increase in viability was observed in the control group after 24 hours (Fig. 1a); additionally, a 7.3% increase was observed at 1 μM (Fig. 1a). In other treatment groups, an increase of 17%, 27%, 36%, 39%, and 44% was observed at 10, 50, 100, 200, and 500 μM, respectively, and a 53% decrease was observed in the 1 mM group (Fig. 1a). Calcein staining revealed minimal levels of cell deterioration (Fig. 1b). In the dexketoprofen-treated groups, a 13% increase in viability was observed in the control group within 24 hours (Fig. 1c); additionally, an increase of 6.6% and 5.1% at 1 and 10 μM were observed (Fig. 1c). In other treatment groups, decreases of 22%, 29%, 33%, 36%, and 38% were observed at 50, 100, 200, 500, and 1 mM, respectively (Fig. 1c). In calcein staining, disruptions in cytoplasmic integrity were observed in the cells (Fig. 1d). Thus, lornoxicam and dexketoprofen affect cell viability in a dose-dependent manner and cause morphological alterations.
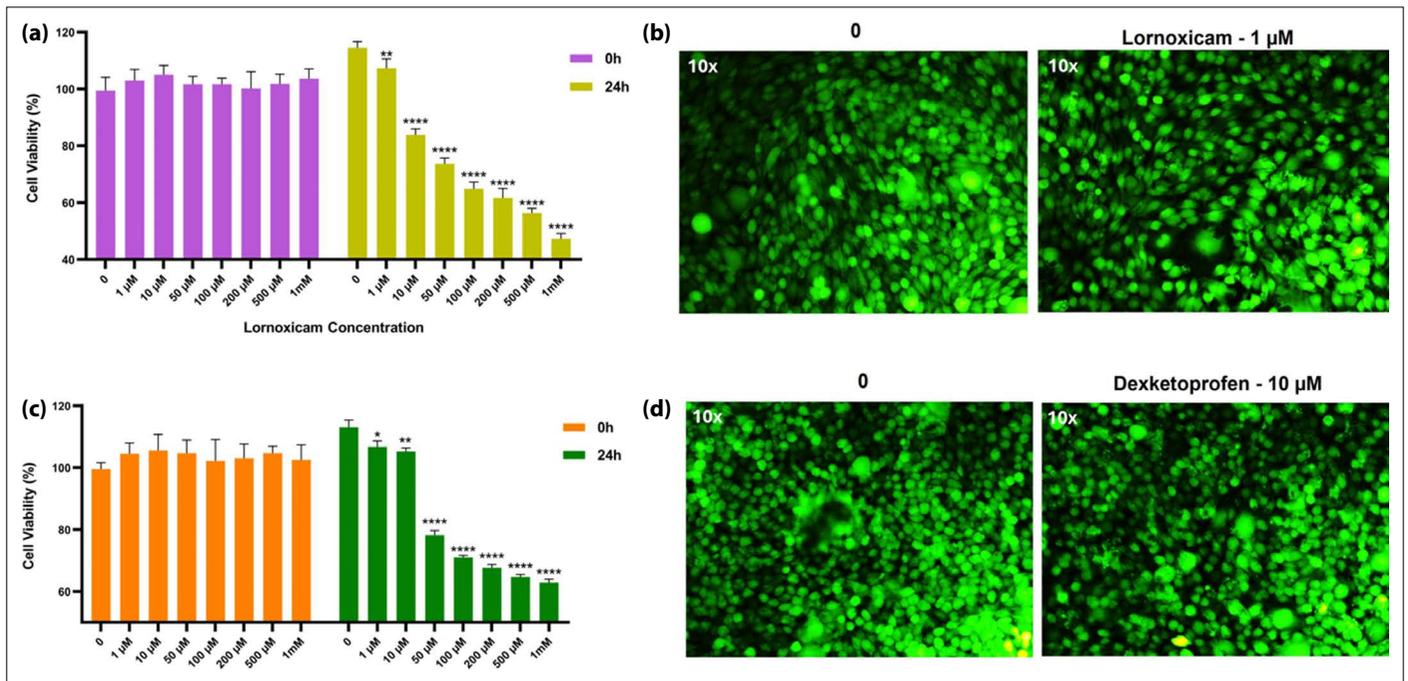
Figure 1. Effects of lornoxicam and dexketoprofen on the viability of L929 cells; percentage viability **(a–c)** and cell morphology **(b–d)** of lornoxicam at doses between 0 and 1 mM after 24 hours of treatment; values are expressed as mean±SD with n=6.
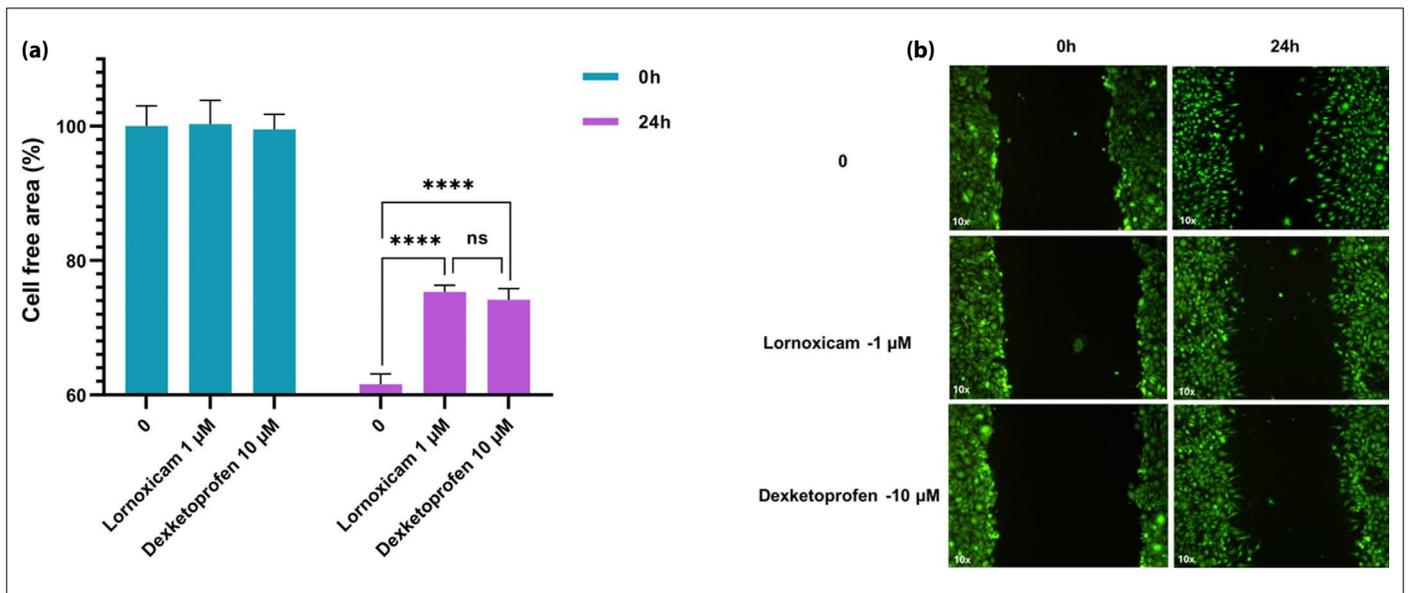

Figure 2. Effects of lornoxicam and dexketoprofen on migration in L929 cells; graph showing the effects of lornoxicam and dexketoprofen at 1 and 10 μM, respectively, on migration after treating the cells for 24 hours **(a)** and microscope image **(b)**; data are presented as mean±SD **(a)**, and values are expressed as mean±SD with n=3.

Lornoxicam and Dexketoprofen Inhibited L929 Cell Migration

Herein, the analyses were conducted to investigate the effects of lornoxicam and dexketoprofen at noncytotoxic concentrations on the migration capacity of fibroblasts. After 24 hours, a closure percentage of 38.5% was observed in the control group (Fig. 2a). In the group treated with 1 μM

of lornoxicam, a closure percentage of 25% was observed, whereas in the group treated with 10 μM of dexketoprofen, the closure percentage was 26% (Fig. 2a). The migration images from which these percentages were calculated are consistent with the data (Fig. 2b). Reportedly, lornoxicam and dexketoprofen reduced the migration ability of L929 cells compared with the control group.
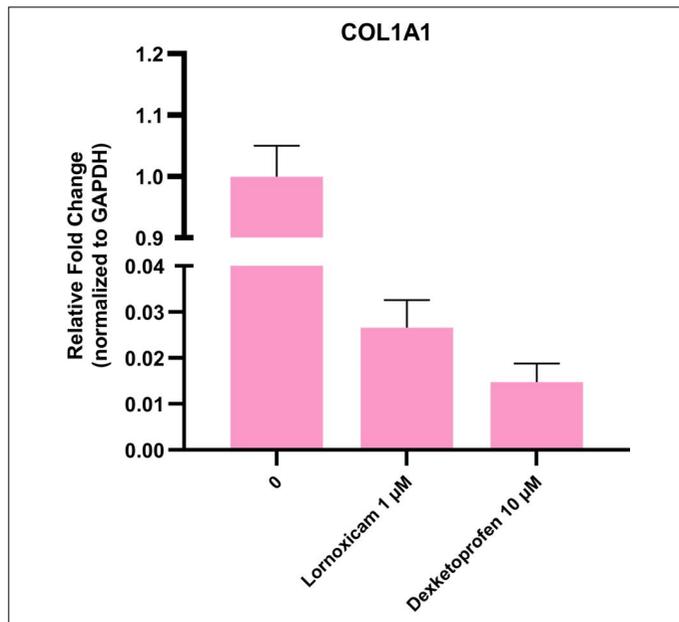
Figure 3. Effects of lornoxicam and dexketoprofen on COL1A1 gene expression L929 cells; Data are presented as mean±SD, and GAPDH genes were used to normalize fold changes.

Lornoxicam and Dexketoprofen Inhibit COL1A1 Expression

The experiments described herein were conducted on a 24-hour day to determine the effects of lornoxicam and dexketoprofen on COL1A1 expression in L929. After 24 hours, COL1A1 expression was 0.027 in the group treated with 1 µM lornoxicam (Fig. 3). When 10 µM of dexketoprofen was applied, 0.015 expression was observed. According to these results, our application doses inhibited COL1A1 gene expression.

Discussion

Lornoxicam and dexketoprofen dose-dependently decreased the viability of fibroblasts and disrupted their morphology. In addition, at doses compatible with viability, they decreased fibroblast migration and COL1A1 gene expression. These two nonselective NSAIDs, even at low doses that do not affect viability, negatively affect healing of fibroblasts by reducing migration and collagen expression. Further molecular studies and comparative evaluations of NSAIDs are needed.

Aspirin (5 mg/well) and diclofenac (0.625 mg/well), nonselective NSAIDs, decreased the proliferation of rat embryo fibroblasts compared with the control group. [16] Aspirin decreases rheumatoid arthritis fibroblast-like synoviocyte proliferation by inhibiting the cell cycle.[17] A dose-dependent decrease in the viability of human tendon cells treated with ibuprofen was observed.[18] Ibuprofen dose-dependently decreased the migration of tendon cells ex vivo and *in vitro* via paxillin.[19] In chondrocytes treated with dexketoprofen trometamol, cell proliferation decreased after 24 hours compared with that in the control group.[20] In a dose-dependent manner, racemic ketoprofen, S(+) enantiomer, and R(-) enantiomer inhibited 3T6 fibroblast proliferation.[21] Prostacyclins reportedly have regulatory functions in fibroblasts in terms of fibrosis, proliferation, and immunity.[22] In such a case, the inhibition of prostacyclin synthesis by NSAIDs may affect the behavior of fibroblasts.[22] Similar to other NSAID studies in the literature, dexketoprofen and lornoxicam dose-dependently decreased the viability of L929 fibroblasts in our study.

Metamizole, an atypical NSAID, dose-dependently decreased fibroblast proliferation and migration; however, it did not considerably alter collagen synthesis.[23] Indomethacin and aspirin suppressed 70%–80% of type II collagen biosynthesis in chondrocytes.[24] In an *in vivo* study investigating wound healing after treatment with diclofenac, it was observed that diclofenac increased wound closure compared with the control group and increased COL1A1 expression in skin tissue compared with the control group.[25] Aspirin, diclofenac, and lornoxicam notably reduced arachidonic acid and collagen-induced CD62 expression in platelets. [26] In an *in vivo* study, the combination of tramadol and acetaminophen or dexketoprofen reduced the counts and immune activation of macrophages similar to fibroblasts. [27] In a study evaluating postoperative adhesion formation in meloxicam- and dexketoprofen-treated rats, meloxicam was found to be effective in the healing process in terms of inflammation, fibroblastic activity, foreign body reaction, collagen formation, and vascular proliferation parameters. [28] In a study examining the effects of dexketoprofen trometamol on incisional wound healing in a rat model, collagen synthesis was negatively affected, even though epithelialization, contraction, and angiogenesis were better in the groups using dexketoprofen.[29] Similar to other NSAIDs, lornoxicam and dexketoprofen had negative effects on fibroblast migration and collagen expression in our study.

Conclusion

Lornoxicam and dexketoprofen affect fibroblast cell viability, migration, and type 1 collagen synthesis. Thus, clinicians should consider these negative effects on fibroblasts during the wound-healing process to ensure the safe use of these drugs. Comparative molecular studies are needed to elucidate the effects of NSAIDs on fibroblasts.

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