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Original Article

Effects of Acetaminophen, Etodolac and Indomethacin on Migration, Proliferation and Collagen Expression of Tendon Cells

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat tendinopathy. Tendon healing requires migration of tendon cells to the repair site, followed by proliferation of these cells and collagen synthesis.

Purpose: This study evaluated the effects of acetaminophen, etodolac, and indomethacin on tenocyte migration, proliferation, and synthesis of type I and III collagen.

Methods: Rat Achilles tendon cells were treated with acetaminophen, etodolac, and indomethacin. Tendon cell migration and proliferation were assessed using transwell filter migration assay and MTT assay, respectively. The expression of collagen I and III mRNA were evaluated by quantitative real-time polymerase chain reaction.

Results: Unlike acetaminophen, etodolac and indomethacin significantly reduced tenocyte migration ($p < 0.05$). No effect of acetaminophen, etodolac, and indomethacin on cell proliferation was observed. The gene expressions of collagen I and III were not affected by acetaminophen, etodolac, or indomethacin treatment.

Conclusion: Acetaminophen has no effect on tendon cell migration, proliferation, and type I and III collagen synthesis. Etodolac and indomethacin, similar to other non-selective NSAIDs, inhibit tendon cell migration but have no effect on tendon cell proliferation and type I and III collagen synthesis. (Tw J Phys Med Rehabil 2014; 42(3): 161 - 169)

Key Words: acetaminophen, etodolac, indomethacin, non-steroidal anti-inflammatory drugs, tendon healing, Acetaminophen, Etodolac, Indomethacin

BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat tendinopathy. NSAIDs modulate the inflammatory process by inhibiting the synthesis of

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prostaglandins (PGs). In addition to their involvement in inflammation and responses to injury, PGs play a key role in bone healing. In the inflammatory stage of the response to tendon injury, PGs, particularly prostaglandin E_2 (PGE_2), are produced in abundance by osteoblasts and accumulate in the fracture callus, creating a microenvironment rich in PG activity. As the tendon repair progresses, PGE_2, prostaglandin I_2 (PGI_2), and thromboxane A2 (TxA_2) stimulate bone resorption by increasing the activity of osteoclasts, with the process ending in bone remodeling and formation. [1] NSAIDs inhibit cyclooxygenases (COX), enzymes that produce PGs. Functionally, NSAIDs reduce the pain and swelling in the acute phase of tendinopathy, and promote early mobilization. [2] However, findings of previous studies suggest that NSAIDs may exhibit undesirable effects on tendon healing, including adverse effects on cell migration, proliferation, and collagen synthesis.[2,3] Therefore, NSAIDs are postulated to negatively affect tissue repair.

Tendon tissue is characterized by a higher proportion of extracellular matrix (ECM) and a relatively low number of cells. Tendons comprise collagen (types I, III, and V) and other matrix molecules, as well as a number of different cells (tenocytes, mast cells, neural elements, and microvascular cells). Tissue ECM and the cellular complement varies along the length of the tendon. [4] The major component of the tendon ECM is type I collagen, assembled in type I collagen fibrils. These collagen fibrils are arranged mainly in the longitudinal direction of the force imposed on the tendon during muscle contraction. [5,6] Type III collagen comprises less than 10% of the tendon and is confined to the endotendineum.

In the initial inflammatory phase of the response to tendon injury, inflammatory cells enter the site of injury. In the regenerative phase that follows within days of injury, tenocytes and fibroblasts in the epitenon migrate to the repair site, proliferate, and mediate tissue repair by synthesizing collagen. Different cells are postulated to contribute via production of different types of collagen at different time points. [7]

Acetaminophen has been widely used for pain control. Although its analgesic mechanism of action involves the inhibition of prostaglandin synthesis, acetaminophen is not considered an NSAID because of a lack of significant anti-inflammatory activity. [8] Its effect of pain mainly comprises blocking of COX-2, primarily in the central nervous system without notable effects in the rest of the body. Long-acting non-selective NSAIDs etodolac and indomethacin are widely used in clinical practice. [9] The effects of NSAIDs ibuprofen and celecoxib on tendon cell migration, proliferation, and collagen synthesis have been investigated in the past [2,3,10-13]. In the current study, we evaluated the effects of acetaminophen, etodolac, and indomethacin on tenocyte migration, cell proliferation, and type I and III collagen synthesis in vitro.

METHODS

All procedures were approved by the Institutional Animal Care and Use Committee.

Primary Culture of Rat Achilles Tendon Cells

The Achilles tendons were excised from 20 Sprague-Dawley rats (weighting 200 to 250 g). The excised tendon was soaked in povidone-iodine for 3 min and washed twice in phosphate-buffered saline (PBS). Each tendon was then cut into small pieces of approximately 1.5–2.0 mm^3 (6 pieces in total from each tendon) and these tendon fragments were individually placed in 6-well culture plates. After 5 min of air-drying to improve adherence, 0.5 mL of Dulbecco's modified Eagle's medium (DMEM; HyClone, Logan, Utah, USA), with 10% fetal bovine serum (FBS; Cansera, Rexdale, Ontario, Canada), 100 U/mL penicillin, and 100 μg/mL streptomycin was added to each well. The explants were then incubated at 37°C in a humidified atmosphere of 5% CO_2/95% air. After migrating out from the explants, the tendon cells grew rapidly and the confluence culture was subcultured using trypsin digestion at a 1:3 dilution ratio. Tendon cells between passages 2 and 4, which showed proper growth rate and a normal fibroblast shape, were used in subsequent studies. All experiments were performed in triplicate.

Transwell Filter Migration Assay

Transwell filters (Costar, Cambridge, MA, USA) with 8.0-μm pores were used for the migration assay. Tendon cells cultured with and without acetaminophen (at 30 and 60 μg/mL doses), etodolac (at 50 and 100 μg/mL

doses), and indomethacin (at 3 and 6 μg/mL doses) for 24 h were seeded at a density of 1.2×10^5 cells per filter. The inner chamber was filled with 250 μL of serum-free DMEM while the outer chamber was filled with 600 μL of DMEM with 10% FBS. Cells were allowed to migrate for 3 h at 37 °C in an atmosphere of 95% air/5% CO_2. The cells were stained with Liu's stain and then washed twice in PBS. Cells on the upper surface of the filter were removed using a cotton swab. The cells on the lower surface of the filter were counted under four random high-power microscopic fields (HPF) (100 × magnification) per filter and the mean number of migrating cells was calculated at each treatment concentration.

MTT Cell Viability Assay

MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; thiazolyl blue) assay was used to evaluate the survival and proliferation of tendon cells after treatment with acetaminophen, etodolac, and indomethacin. The cells were seeded into 24-well flat-bottomed culture plates. Acetaminophen, etodolac, and indomethacin were added to the culture dish at the following concentrations: acetaminophen at 0 (control group), 30, and 60 μg/mL; etodolac at 0, 50, and 100 μg/mL; and indomethacin at 0, 3, and 6 μg/mL. After incubation for 24 h, the cells were observed under a microscope and the MTT assay was performed. DMEM, containing 50 μg/mL MTT, was added to each well and the plates were incubated at 37 °C in an incubator for 1 h. MTT solution was discarded and 1 mL of dimethyl sulfoxide (DMSO) was added to each well. The colorless DMSO turned purple after the formazan crystals were dissolved by mixing using the micropipette. Aliquots were transferred from the wells into a 96-well plate and optic density (OD) was read immediately at 570 nm by using a spectrophotometer (NanoDrop 1000, Thermo scientific, Wilmington, DE). Relative fold changes in OD_{570} nm value for three-drug-treated cells to the control cells were calculated.

Quantitative Real-Time Polymerase Chain Reaction (RT-PCR) Analysis

Total RNA was extracted from tendon cells by using solution D (1 mL of solution D per 107 cells) according to the manufacturer's instructions. Proteins and genomic DNA were removed by extraction of total RNA with phenol and chloroform/isoamyl alcohol (49:1). Complementary (c) DNA was synthesized using 1 mg of total RNA in 20 mL of RT reaction mix containing 0.5 mg of random primers, 0.8 mM dNTPs, 0.1 M DTT, and 1 L of first-strand buffer. Quantitative RT-PCR was performed using SYBR Green and MxPro-Mx3000P QPCR machine (Stratagene, NeoMarkers, Fremont, CA, USA). Aliquots (20 ng) of cDNA were used for each quantitative RT-PCR reaction, with each reaction performed in triplicate. The relative mRNA level between experimental groups was calculated using MxPro software (Stratagene) with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) used as an internal control. Changes in mRNA level were reported as multiples of increases relative to the untreated controls. The oligonucleotide sequences of specific primers used in this study are presented in Table 1.

Table 1: Oligonucleotide sequences for the specific primers used in real-time PCR

GADPH	Sense: AGTCTACTGGCGTCTTCA
	Antisense: TTGTCATATTTCTCGTGGT
Type I collagen	Sense: TGGAGACAGGTCAGACCTG
	Antisense: TATTCGATGACTGTCTTGCC
Type III collagen	Sense: TAAAGGGTGAACGGGGCAGT
	Antisense: ACGTTCCCCATTATGGCCAC

Statistical Analysis

All data are expressed as mean ± SEM. Comparisons of migration assay and MTT assay results between the control cells and cells treated with acetaminophen, etodolac, and indomethacin were performed using Kruskal-Wallis test. Mann-Whitney test was used to identify significant findings; p value less than 0.05 was considered statistically significant.

RESULTS

The transwell migration assay was used to investigate the effect of acetaminophen, etodolac, and indomethacin on tenocyte migration in vitro. We observed an inhibitory effect of acetaminophen (0.71 ± 0.14 and 0.72 ± 0.25-fold change relative to the controls in cultures treated with 30 and 60 μg/mL of acetaminophen, respectively), etodolac (0.37 ± 0.19 and 0.26 ± 0.16-fold change relative to the controls in cultures treated with 50 and 100

μg/mL of etodolac, respectively), and indomethacin (0.25 ± 0.08 and 0.24 ± 0.04-fold change relative to the controls in cultures treated with 3 and 6 μg/mL of indomethacin, respectively) on tenocyte migration (Figure 1). The inhibitory effects of etodolac and indomethacin were statistically significant ($p < 0.05$), but the effect of acetaminophen was minor without statistical significance.

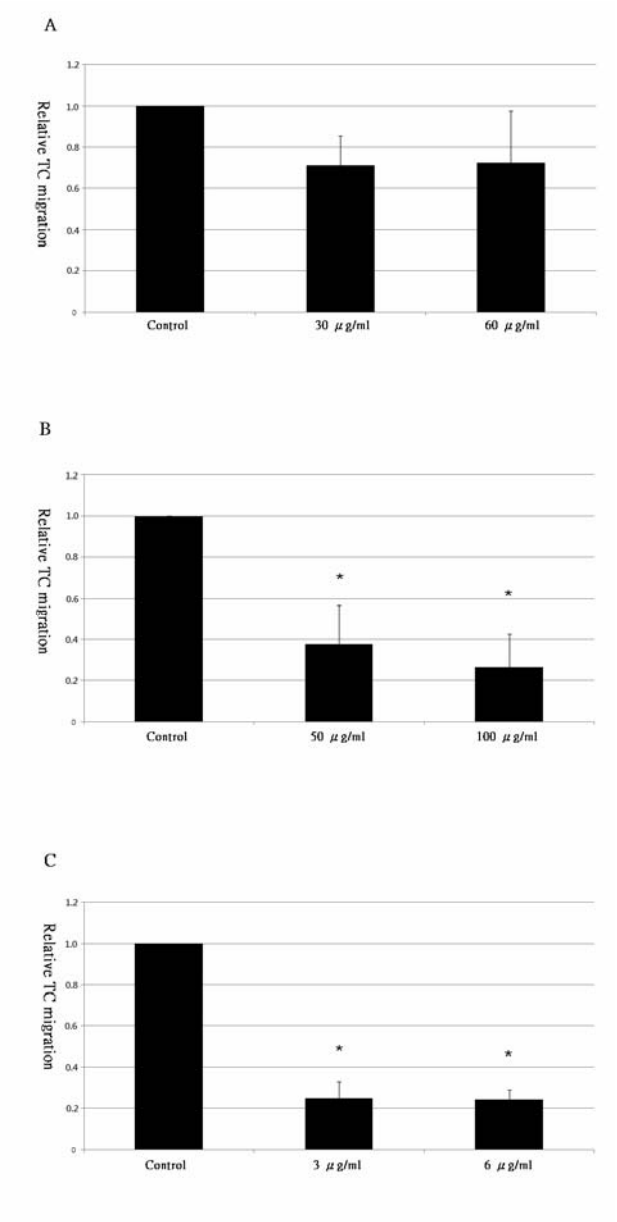

Figure 1: Inhibitory effect of tendon cells migration in vitro after treating with (A) acetaminophen (B) etodolac (C) indomethacin. The inhibitory effect was significant after etodolac and indomethacin treatment (*p<0.05)

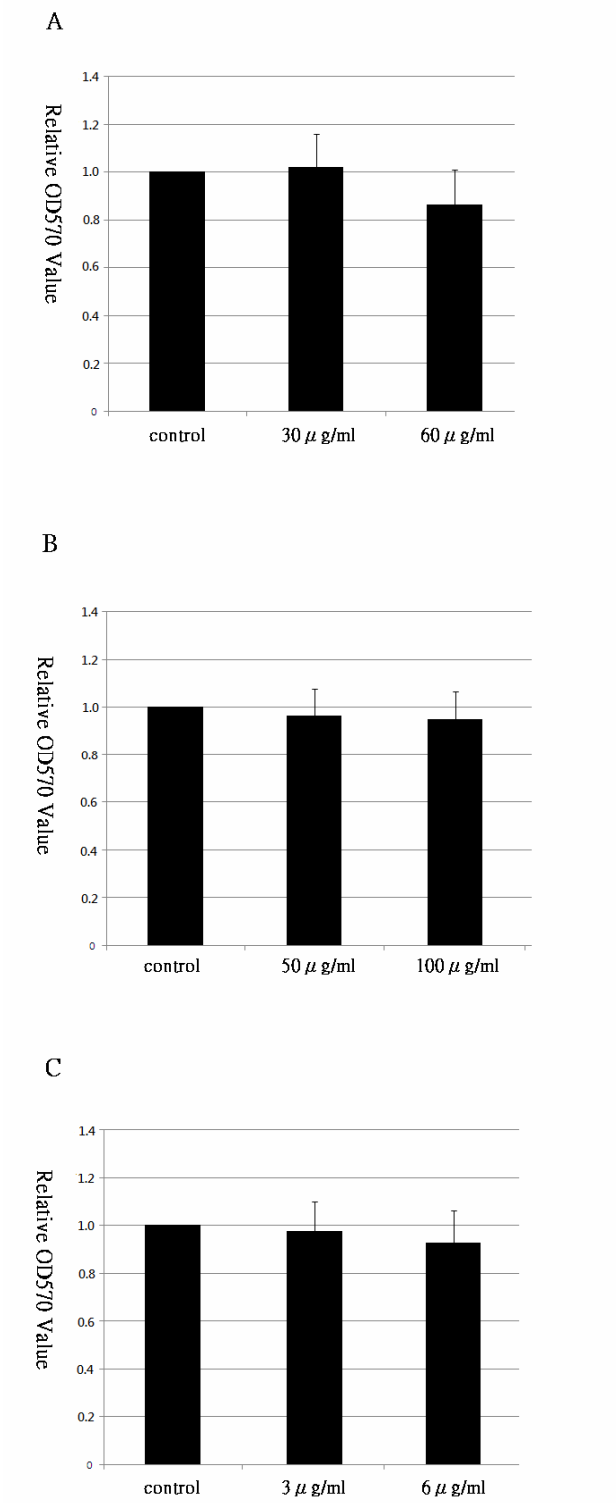

Figure 2: MTT assay revealed constant OD_{570} value as functions of (A) acetaminophen (B) etodolac (C) indomethacin

The MTT assay for tendon cell viability revealed that the OD_{570} value remained constant after treatments

with acetaminophen (1.02 ± 0.13 and 0.86 ± 0.15-fold change relative to controls in cultures treated with 30 and 60 μg/mL of acetaminophen, respectively), etodolac (0.97 ± 0.11 and 0.95 ± 0.12-fold change relative to controls in cultures treated with 50 and 100 μg/mL of etodolac, respectively), and indomethacin (0.98 ± 0.12 and 0.93 ± 0.13-fold change relative to controls in cultures treated with 3 and 6 μg/mL of indomethacin, respectively), as shown in Figure 2.

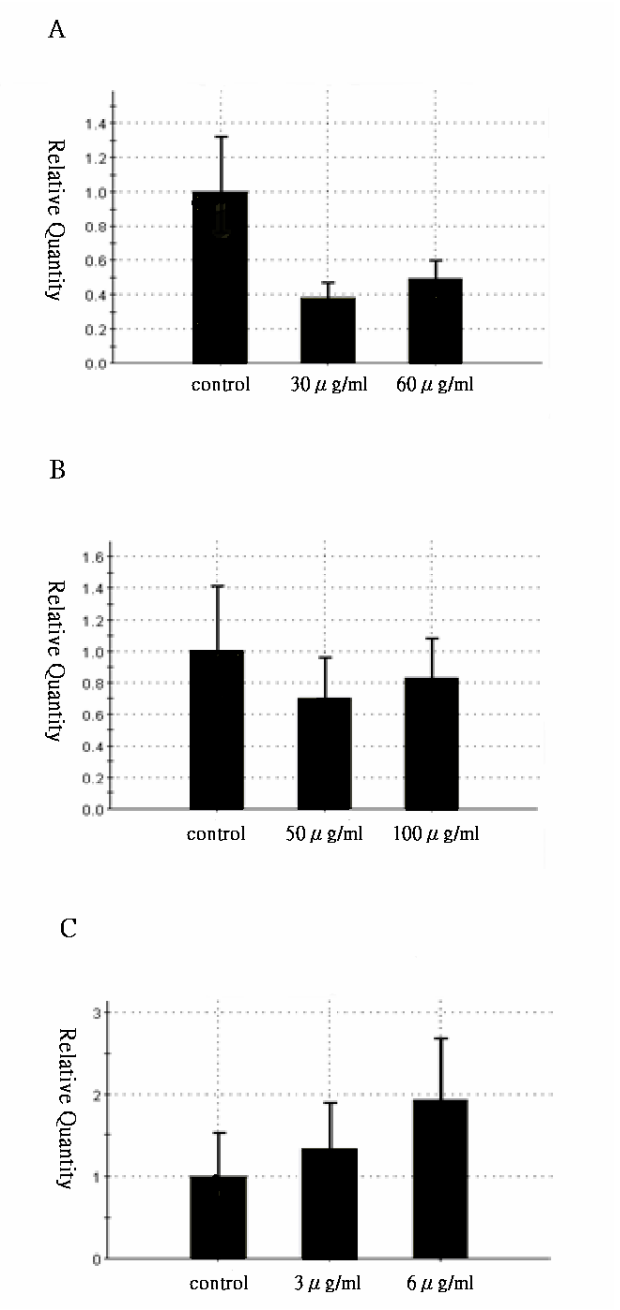

Figure 3: Type I collagen in drug-treated tendon cells were analyzed by real-time RT-PCR. Relative quantity of collagen I mRNA after treated with (A) acetaminophen (B) etodolac and (C) indomethacin varied without statistical significance.

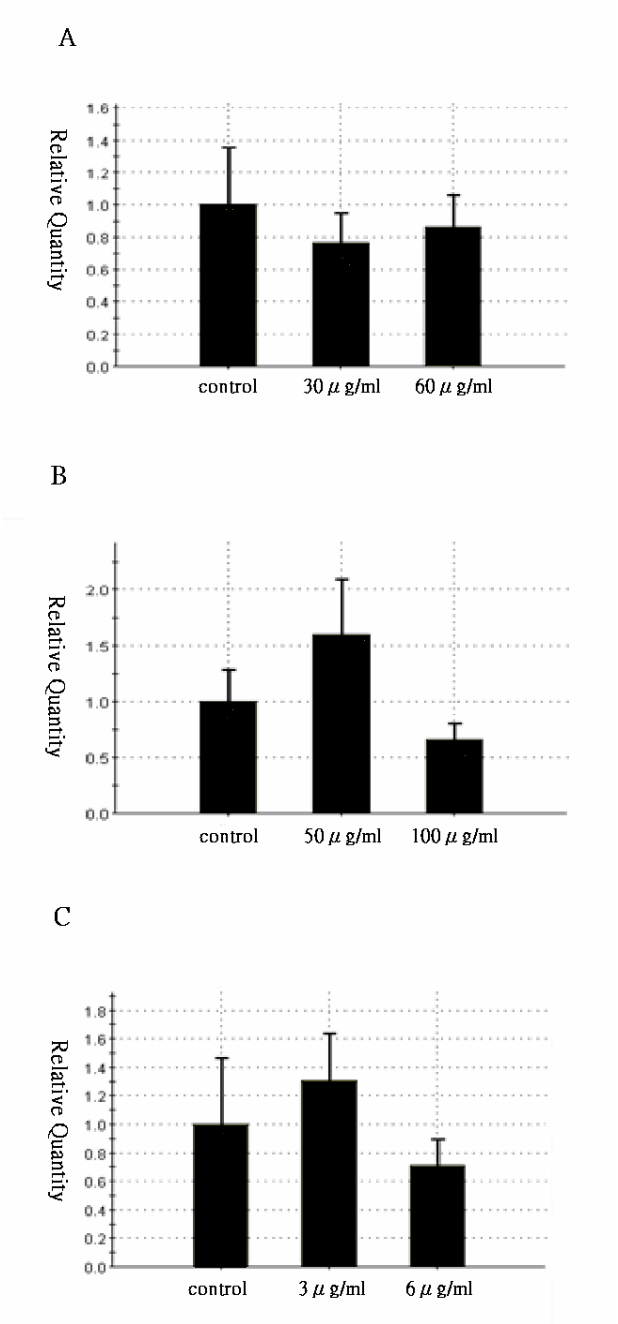

Figure 4: Type III collagen in drug-treated tendon cells were analyzed by real-time RT-PCR. Relative quantity of collagen III mRNA after treated with (A) acetaminophen (B) etodolac and (C) indomethacin varied without statistical significance.

To investigate the alterations in the transcription of type I and III collagen, mRNA expressions of type I and

III collagen in tendon cells treated with acetaminophen, etodolac, or indomethacin were analyzed using qPCR. The mRNA levels of collagen I and III remained constant after treatment with all the studied drugs (Figures 3 and 4).

DISCUSSION

Healing of the injured tendon proceeds through three overlapping phases: inflammation, regeneration, and remodeling/maturation. [14] The initial phase involves an inflammatory response with an influx of inflammatory cells to the site of injury. Recent studies evaluating rotator cuff tears in humans and in animal models, for example, have demonstrated an increased infiltration of neutrophils, macrophages, and mast cells. [15] The macrophages secrete transforming growth factor b1 (TGF-β1), which stimulates collagen formation and proteinase activity. [15] During the regenerative phase, tenocytes from the epitendon and endotendon migrate to the repair site and proliferate. The activation of fibroblasts results in increased expression of a number of cytokines, including insulin-like growth factor-I (IGF-I), connective tissue growth factor (CTGF), IL-6, basic fibroblast growth factor (bFGF), platelet-derived growth factor-β (PDGF-β), bone morphogenic protein (BMP)-12, BMP-13, and BMP-14. [5,15,16] Expression of BMP-12, BMP-13, and BMP-14 by fibroblasts has been demonstrated to play an integral role in the induction of neotendon and ligament formation and improvement of the healing of tendon laceration. [15] Finally, the production of ECM, composed mostly of collagen, begins once a sufficient number of tendon cells have colonized the repair site. Initially, type III collagen is rapidly deposited in a woven pattern for the first few weeks following injury. [7] The remainder of the repair process is characterized by a progressive transition to the deposition of type I collagen, which continues for an indeterminate period in the final maturation phase. [2,17] Tenocyte migration, proliferation, and synthesis of type I and III collagen are, therefore, crucial elements of the healing process in the injured tendon.

Acetaminophen is often used in clinical practice for pain control. Unlike NSAIDs, acetaminophen has little effect in the peripheral tissue. In previous studies, no obvious inhibitory effect of acetaminophen was observed on cell migration, proliferation, and type I and III collagen synthesis. In line with past reports, we observed no inhibitory effects following acetaminophen treatment in this study. However, long-term acetaminophen use was shown to inhibit collagen cross-linking and reduce tissue water, contributing to decreased tendon stiffness. [18] Other reports revealed that a high dose of acetaminophen (4,000 mg/day) taken orally during 12 wk of knee extensor resistance training in humans results in tendon hypertrophy, decreased tendon stiffness, and increased strain. [19] Acetaminophen was also reported to enhance IL-6 production in tendons after exercise, resulting in the accumulation of this cytokine in the peritendinous space. Interleukin-6 is produced by tendon during exercise and is a potent stimulator of collagen synthesis. IL-6 may also contribute to alterations in extracellular matrix turnover. [20] In our study, acetaminophen had no effect on tendon cell migration, proliferation and collagen I and III synthesis, but the possible inhibitory effect on tendon might due to collagen cross-linking inhibition or alterations in extracellular matrix turnover. The possible effect of acetaminophen on tendon cells, therefore, warrants further investigation.

In previous studies, both non-selective NSAIDs and selective COX-II inhibitors were reported to inhibit cell migration and proliferation. Ibuprofen was shown to inhibit cell migration and proliferation by altering prostaglandin metabolism, [21] while upregulating the expression of collagenase enzymes. [12] Indomethacin was found to inhibit cell migration by reducing cellular calcium influx. [22] The effect of NSAIDs on collagen synthesis is controversial at this time, with some studies reporting an increase in type I, II, and III collagen expression, [23,24] while other studies reporting no effect on collagen synthesis. [25,26] Our current study suggests that long-acting non-selective NSAIDs (etodolac and indomethacin) inhibit tenocyte migration; however, NSAIDs had no significant effects on tendon cell proliferation and type I and III collagen synthesis. The putative inhibitory effect of NSAIDs on tendon healing may therefore be mediated by their modulation of other aspects of tissue repair, such as matrix metalloproteases (MMP) or collagen cross-linking. [12]

The peak plasma concentrations of acetaminophen, etodolac, and indomethacin were reported to reach up to

25, 45, and 2 μg/mL respectively. In our study, the concentration of acetaminophen (30 μg/mL), etodolac (50 μg/mL) and indomethacin (3 μg/mL) were similar to the peak concentraions in human plasma after taking theraputic dose. In order to making our dose more clinically relevant, we chose these three concentrations for experimental use.

Based on our in vitro findings, long-acting non-selective NSAIDs such as etodolac and indomethacin may adversely affect tendon healing. In contrast to the NSAIDs, acetaminophen had less of an effect on the tendon healing process. With regard to the application of in vitro findings to in vivo situations, non-selective NSAIDs and COX-II inhibitors should be used with caution in the acute phase of tendon healing. Our findings suggest that acetaminophen is relatively safe for use during tendon healing, but it exhibits mild pain-relieving and anti-inflammatory effects.

CONCLUSION

In conclusion, acetaminophen did not affect tendon cell migration, proliferation, or synthesis of type I and III collagen. Etodolac and indomethacin, similar to other non-selective NSAIDs, inhibited tendon cell migration, but elicited no effect on tendon cell proliferation and type I and III collagen synthesis.

COMPETIBG INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Wen-Chung Tsai and Jong-Hwei S Pang are responsible for ideation and experimental instruction. Yun-Ming Yang, Hsiang-Ning Chang and Chung-Bao Hou are responsible for experimental procedures. Yun-Ming Yang and Chia-Ying Hsu are responsible for data analysis and manuscript writing.

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非類固醇抗炎藥物對肌腱纖維細胞移行、增生及膠原蛋白合成的影響

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背景：非類固醇抗炎藥物(NSAID)常被使用在肌腱發炎的情況。此類藥物因可抑制環氧合酶(COX)的活性，可以減輕患部的腫脹疼痛，並可促進及早活動。但有先前研究顯示，非類固醇抗炎藥物(NSAID)如 celebrex，ibuprofen 會抑制肌腱纖維細胞的移行，增生及合成膠原蛋白，進而有礙於患處的復原。

目的：本實驗選擇檢測非典型 NSAID (acetaminophen)及非選擇性長效 NSAID (etodolac、indomethacin)對肌腱纖維細胞移行、增生及膠原蛋白合成的影響。

方法：大鼠肌腱細胞經加入藥物培養後，運用細胞遷移實驗(transwell filter migration assay)以及細胞存活率分析(MTT assay)來檢測纖維母細胞的移行及增生。並使用即時定量聚合酶連鎖反應(real-time polymerase chain reaction)來檢測第一型及第三型膠原蛋白之合成。

結果：細胞遷移實驗中，etodolac 組和 indomethacin 組纖維母細胞之移行個數明顯降低，此抑制效果具統計學上意義；Acetaminophen 組纖維母細胞移行個數與對照組相較無變化。細胞存活率分析和即時定量聚合酶連鎖反應中，Acetaminophen 組、etodolac 組和 indomethacin 組纖維母細胞增生率和第一型或第三型膠原蛋白合成，與對照組相較無變化。

結論：Acetaminophen 對於肌腱纖維母細胞的移行、增生及膠原蛋白合成無影響。而 etodolac 和 indomethacin 則與其他非選擇性非類固醇抗炎藥物相同，對於細胞的遷移有抑制效果，而對細胞增生或膠原蛋白合成則無影響。（台灣復健醫誌 2014；42(3)：161 - 169）

關鍵詞：對乙醯氨基酚(acetaminophen)，依托度酸(etodolac)，吲哚美辛(indomethacin)，非類固醇抗炎藥物(non-steroidal anti-inflammatory drugs)，肌腱癒合(tendon healing)

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