Rehabilitation Practice and Science

Volume 49
Issue 2 *Taiwan Journal of Physical Medicine and Rehabilitation (TJPMR)*

Article 5

12-31-2021

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Hang-Ming Chen

Zhi-Jia Chen

Li-Ping Lin

Wen-Chung Tsai

Jong-Hwei S. Pang

Recommended Citation

Chen, Hang-Ming; Chen, Zhi-Jia; Lin, Li-Ping; Tsai, Wen-Chung; and Pang, Jong-Hwei S. (2021) "Celecoxib Did Not Impair Proliferation, Migration and F-actin Formation of Skeletal Muscle Cells," *Rehabilitation Practice and Science*: Vol. 49: Iss. 2, Article 5.
DOI: https://doi.org/10.6315/TJPMR.202112_49(2).0005
Available at: https://rps.researchcommons.org/journal/vol49/iss2/5

Original Article

Celecoxib Did Not Impair Proliferation, Migration and F-actin Formation of Skeletal Muscle Cells

Hang-Ming Chen[1], Zhi-Jia Chen[2], Li-Ping Lin[1,3], Wen-Chung Tsai[2,4], Jong-Hwei S. Pang[1,3]

[1] Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Linkou;
[2] Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Taoyuan;
[3] Graduate Institute of Clinical Medical Sciences, Chang Gung University, Taoyuan;
[4] College of Medicine, Chang Gung University, Taoyuan.

Muscle injury is the most common sport related soft-tissue injury. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for muscle injury treatment. The newest guideline (PEACE and LOVE) from British Journal of Sports Medicine in 2019 emphasized the avoidance of anti-inflammatory modalities in acute phase for the concerning about the negative effect on long-term tissue healing. It has been investigated that NSAIDs impeded cell migration which is crucial role in muscle healing. This study was designed to determine the effects of celecoxib, one of the cyclooxygenase-2 (COX-2) inhibitor on cell proliferation and migration in skeletal muscle cells. MTT assay (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) was used to examine cell viability. In vitro wounding healing test, transwell filter migration assay and F-actin staining were adopted to evaluate cell migration and spreading. The results showed that celecoxib had no negative effect on in vitro wounding healing test and cell viability. Besides, celecoxib also did not impact cell migration and cell spreading. Despite the "PEACE and LOVE" guideline, celecoxib might be the better choice compared to the traditional NSAIDs for some inevitable situation due to their possible less influence on the muscle recovery process. (Tw J Phys Med Rehabil 2021; 49(2): 183 - 192)

Key Words: Celecoxib, skeletal muscle cells

INTRODUCTION

Among the general population, muscle injuries are one of the most common traumas in sports. The incidence rate ranged from 10% to 55% of all the sustained injuries.[1] In a previous study, 37% of male professional football players missed training or competition due to injuries of muscle.[2] For the elite international player, muscle damages account for even 40.9% of all recorded injuries, with 57.5% of them resulting in the lost of time.[3]

For the past few years, traditional treatments to immediate soft tissue injury included protection, optimal

Submitted date: 21 May 2021 Revised date: 25 July 2021 Accepted date: 27 July 2021
Correspondence to: Jong-Hwei S. Pang, PhD, Graduate Institute of Clinical Medical Sciences, Chang Gung University 259, Wen-Hwa 1st Road, Gueishan Township, Taoyuan City 333, Taiwan.
Tel：(03) 2118800 ext. 3482 E-mail：jonghwei@mail.cgu.edu.tw
doi: 10.6315/TJPMR.202112_49(2).0005

loading, ice compression, and elevation (the acronyms "POLICE" guideline),[4] the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and physical therapy.[1,5] The major effects of NSAIDs are anti-inflammatory, analgesic and antipyretic activity, and they are among the most widely used drugs in the world.[6] NSAIDs act as a cyclooxygenase (COX) inhibitor, which reduces prostaglandin production from arachidonic acid. Decreased prostaglandin level limits the inflammatory and edema responses after injury.[7,8] However, recent studies have shown the beneficial effects of inflammatory cells on muscle healing.[9] The newest acronym guideline evolved with this trend to the Protect, Elevate, Avoid anti-inflammatory modalities, Compress, Educate, Load, Optimism, Vascularisation, Exercise (PEACE &LOVE) in 2019. It emphasizes the avoidance of anti-inflammatory modalities for the concerning about the negative effect on long-term tissue healing, especially with higher dosages. And the use of NSAIDs should be excluded in the standard care programs.[10]

There are 2 structurally distinct forms of the cyclooxygenase namely COX-1 and COX-2. COX-1 is contained in most normal cells and COX-2 is induced mainly in inflammatory cells.[11] Thus NASIDs are grouped by their selectivity for inhibition of COX-1 and COX-2 into: (1) non-selective (ns-NSAIDs), and (2) selective NSAIDs (s-NSAIDs) with preferential inhibition of COX-2 isozymes.[12] In the traditional ns-NSAIDs spectrum, Flurbiprofen showed either a delayed or insufficient regeneration of the muscle cells after the injury.[13] Piroxicam-treated rabbit model revealed degeneration delay to the damaged tissue and the slowed regeneration of muscle tissue at the injury site.[14] Besides, a recent study demonstrated ibuprofen may impair the migration of skeletal muscle cells by downregulating protein expression.[15] As to another spectrum, NS-398, a cyclooxygenase-2-specific inhibitor, decreased both proliferation and maturation of differentiated myogenic precursor cells.[16] Our previous study showed celecoxib inhibited tendon cell migration and proliferation.[17] And a recent systemic review demonstrated a perioperative use of celecoxib may inhibit tendon-to-bone healing after rotator cuff repairing procedure.[18] COX-2 inhibitors have become a much frequent used medication, for the elder people with multiple comorbidities. It's crucial to evaluate how COX-2 inhibitors impede the healing process of injured muscle.

After muscle fibers are injured, the nuclei in the damaged area often began apoptosis.[19] Muscle regeneration relies mainly on its resident muscle satellite (stem) cells.[20,21] Satellite cells are located outside the myofiber plasma membrane and beneath the surrounding basal lamina, and normally exist in a quiescent state.[21,22] When encountered muscle injury, satellite cells are activated and migrate to the lesion sites, proliferate into structures called myotubes and then fuse with the injured fiber to repopulate the nuclei lost.[21] Satellite cells are also important in regulating the activity of fibroblasts, which are crucial for extracellular matrix (ECM) synthesis and remodeling.[23] Therefore, cell proliferation and migration play imperative role in muscle healing. Recent study showed traditional NSAID such as ibuprofen impaired the migrated ability of muscle cells by decreasing the expression of p130cas and CrkII which involved in cell migration process.[15] But studies about the COX-2 inhibitors on cell migration have never been reported.

Taken together, establishing a research to evaluate the hypothesis, that COX-2 inhibitors impede the healing process of injured muscle is very crucial. We cultured rat gastrocnemius muscle cells as the wound healing model to conduct an in vito study. The main purpose of this study is to find out the effect and molecular mechanism of celecoxib, a common COX-2 inhibitors, on proliferation and migration of skeletal muscle cells.

MATERIALS AND METHODS

Animals

Sprague-Dawley rats (weighing 200 to 250 gm) were purchased from Bio Lasco Taiwan Co. Ltd. All experimental methods were approved by the Institutional Animal Care and Use Committee of Chang Gung University, Taiwan (IUCAC no. CGU107-136) and were compliant with Guide for Laboratory Animal Facilities and Care as promulgated by the Council of Agriculture. Executive Yuan, ROC. Taiwan.

Primary culture of rat gastrocnemius muscle cells

The gastrocnemius muscle was excised from Sprague-Dawley rats. The isolation method to obtain primary culture of skeletal muscle cells was referenced by Liao et al.[15] Briefly, the muscle was cut into small pieces and treated with 0.2% collagenase type I for 45 minutes at 37 ºC and following treated with 0.25% trypsin-EDTA for another 45 minutes. After centrifuged, cell pellets were re-suspended with growth medium (Dulbecco's modified Eagle's medium (DMEM) with 10 % fetal bovine serum, 5% chick embryo extract, and 100 U/ml penicillin, and 100 g/ml streptomycin (Gibco, Thermo Fisher Scientific, Waltham, MA, USA) and seeded on plate. After plating 1 hour, the supernatant containing skeletal muscle cells were transferred to another plate and incubated at 37°C in a humidified atmosphere of 5 % CO2/95 % air. Skeletal muscle cells were cultured in a 10 cm culture plate with growth medium and these cells were used for the following experiment.

In vitro wound healing model

Cells were seeded on 6-well dishes and grow to in a monolayer. The cells were treated with celecoxib (0.8, 2.0, 4.0, and 8.0 μg/ml) for 24 hours, and then scraped with a sterile pipette tip to consistently create a linear cell-free zone (1 mm in diameter) on the wells. The wells were photographed at 0 and 12 hours after celecoxib treatment. The width of the cell-free zone was separately quantified by Image-Pro Premier software (Media Cybernetics, Rockville, MD, USA).

Cell viability test

Cells were treated with celecoxib (0.8, 2.0, 4.0, and 8.0 μg/ml) for 24 hours. MTT reagent (3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) (Sigma-Aldrich, St. Louis, MI, USA) (50 μg/ml) was added into well and incubated at 37°C. The supernatant was removed and the formazan crystals was dissolved by dimethyl sulfoxide (DMSO) one hour later. Aliquots were detected at 595 nm by a spectrophotometer (VICTORTM X3, PerkinElmer Inc., Waltham, MA, USA).

Transwell filter migration assay

Skeletal muscle cells were treated with celecoxib with different concentrations (0.8, 2.0, 4.0, 8.0 μg/ml) for 24 hours, and then the cells (1×10^5 cells per well) were seeded in 200μl serum-free DMEM on the transwell filter (#3464, Costar, Corning, Cambridge, MA, USA). Cells were allowed to migrate for 3 hours at 37°C in an atmosphere of 95% air/5% CO2. The cells were stained with Liu's stain and non-migrating cells on the upper surface of the filter were removed using a cotton swab. The migrated-cells on the lower surface of the filter were observed by a microscope (200x) (Eclipse Ni-U; Nikon, Japan) and the mean number of migrated cells were counted for each concentration.

Cell spreading assay and immunofluorescence staining

Cells were treated with celecoxib (0.8, 2.0, 4.0, and 8.0 μg/ml) for 24 hours, and then cells were seeded on 6-well culture dishes with DMEM containing 20% FBS. After plating for 30 minutes, cells were fixed in 10% formalin for 15 minutes, washed 3 times in PBS, and incubated in blocking solution (3% BSA in PBS) for 30 minutes. The cells were incubated for 1 hour with phalloidin conjugated FITC (Sigma, St. Louis, MO, USA). After washed in PBS, cells were stained in PBS containing 1 μg/ml DAPI for 5 min. The spread cells were observed under ZOE™ Fluorescent Cell Imager (175x) (Bio-Rad, Hercules, CA, USA). Three randomly selected fields were for observed and calculated.

Statistical analysis

The numerical results were presented by the mean ± standard error of the mean (S.E.M). The data was further analyzed by Kruskal-Wallis test to compare differences between groups. and. If there was a statistical significance between groups, a Mann-Whitney test was subsequently applied to detect where the difference existed. A p-value < 0.05 was considered statistical significant. All experiments were repeated in triplicate (n = 3).

RESULTS

Celecoxib had no influence on in vitro wound healing of skeletal muscle cells

To study whether celecoxib has an inhibitory effect on the skeletal muscle cells, we used in vitro wound

healing model. A confluent monolayer of skeletal muscle cells was made and treated with different concentrations of celecoxib for 24 hours. As shown in figure 1(A), there were no difference between control cells and celecoxib-treated skeletal muscle cells. The relative wound healing rates were 100.0 ±4.2%, 99.4 ±1.5%, 104.4 ±1.4%, 103.9 ±4.7%, and 87.6 ±5.2% in the control and 0.8, 2, 4, and 8 μg/ml celecoxib-treated cells, respectively ($p>0.05$, figure 1(B)).

Celecoxib had no impact on the number of viable skeletal muscle cells

In order to investigate cell proliferation, skeletal muscle cells were treated with different concentrations of celecoxib for 24 hours. MTT assay illustrated no significant difference between different concentrations of celecoxib-treated skeletal muscle cells. The relative cell counts were 100.0±3.6%, 101.4±2.6%, 99.9±1.7%, 102.6±2.2%, and 101.4±1.9 % in the control and 0.8 μg/ml, 2 μg/ml, 4 μg/ml, and 8 μg/ml celecoxib-treated cells, respectively ($p>0.05$, figure 2).

Celecoxib had no effect on migration of skeletal muscle cells

Skeletal muscle cells were treated with different concentrations of celecoxib for 24 hours. Migration assay demonstrated that celecoxib had no effect on migration of skeletal muscle cells (figure3(A)). The relative cell migration rates were 100 ±1.6%, 101.5 ±3.3%, 99.8 ±3.4%, 104.0 ±4.2%, and 107.9 ±3.0% in the control and 0.8 μg/ml, 2 μg/ml, 4 μg/ml, and 8 μg/ml in celecoxib groups, respectively ($p>0.05$, figure 3(B)).

Celecoxib had no hindrance on cell spreading of skeletal muscle cells

Cell spreading is one of the crucial steps in cell migration. Cell spreading was visualized by performing F-actin staining. The result demonstrated there were no effect on cell spreading of celecoxib-treated cells (figure 4(A)). The relative cell spreading rates were 94.0 ±0.5%, 92.1 ±0.8%, 93.6 ±1.0%, 92.6 ±1.1%, and 92.8 ±0.6% in the control and 0.8 μg/ml, 2 μg/ml, 4 μg/ml, and 8 μg/ml in celecoxib groups, respectively ($p>0.05$, figure 4(B)).

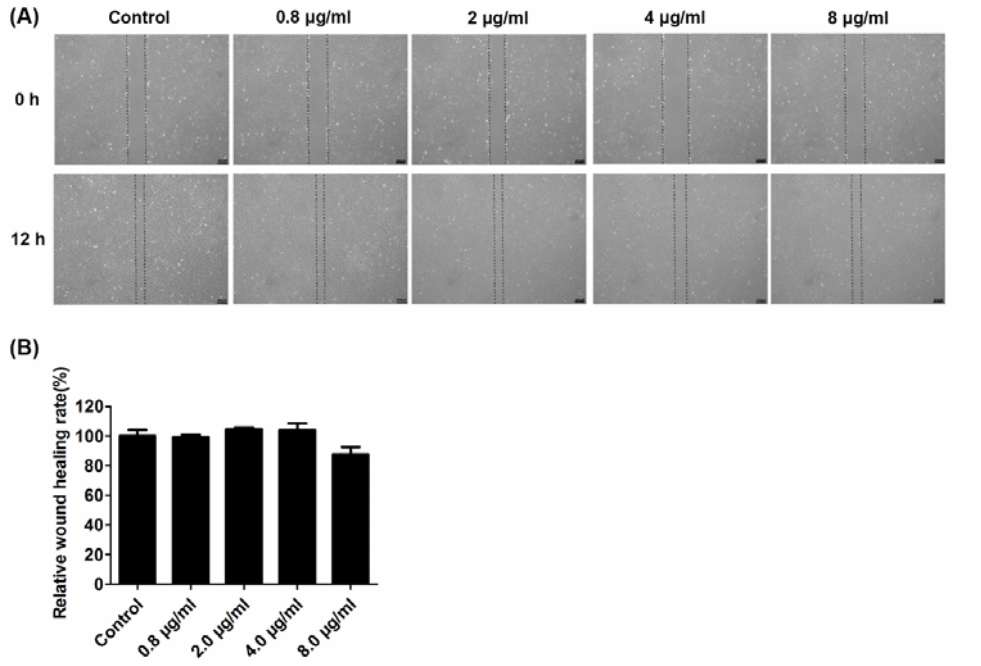

Figure 1. In vitro wound healing.

A monolayer of skeletal muscle cells were treated with 0.8 μg/ml, 2 μg/ml, 4 μg/ml, and 8 μg/ml celecoxib. After 24 hours, the cells were scratched to produce a linear, cell-free zone. The cell-free zones were photographed at 200x and are indicated by the black dotted lines (A). The relative wound healing rate was calculated as the ratio of the remaining width of the cell-free zone at 12 hours compared to the original width at 0 hours (B), the data represented mean ± SEM of three independent experiments. *mean $p<0.05$ compared to control. Scale bars, 200 μm.

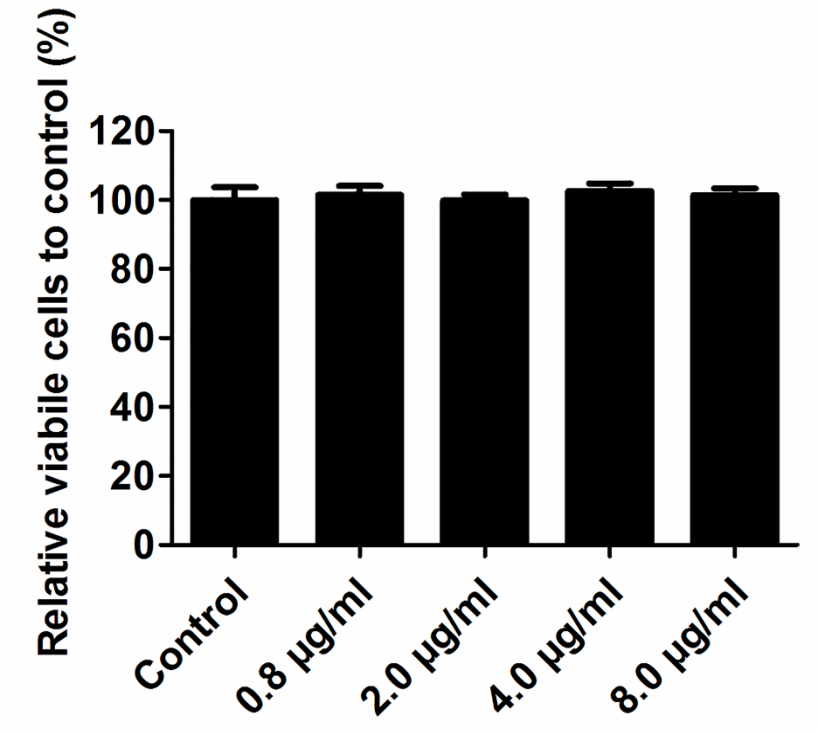

Figure 2. Effects of celecoxib on cell proliferation.

Skeletal muscle cells were treated with 0.8 μg/ml, 2 μg/ml, 4 μg/ml, and 8 μg/ml celecoxib for 24 hours and cell viability was determined by the MTT assay. Data represented the mean ± SEM of three independent experiments.

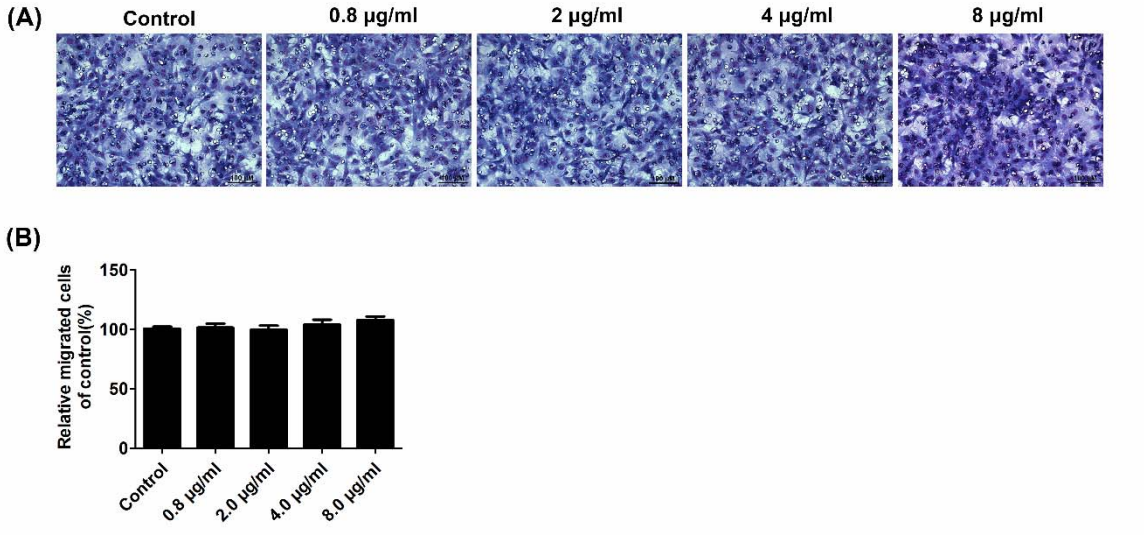

Figure 3. Effects of Celecoxib on migration ability of skeletal muscle cells.

Skeletal muscle cells were treated with 0.8 μg/ml, 2 μg/ml, 4 μg/ml, and 8 μg/ml celecoxib for 24 hours. The cell migration was assessed by transwell filter migration assay. The cells migrating across the filter were stained by Liu's stain. The cytoplasm was stained red, and the nucleus was stained blue (A). The relative percentage of the migrated cells was shown in (B), and the data represented the mean ±SEM of three independent experiments. Scale bars, 100 μm.

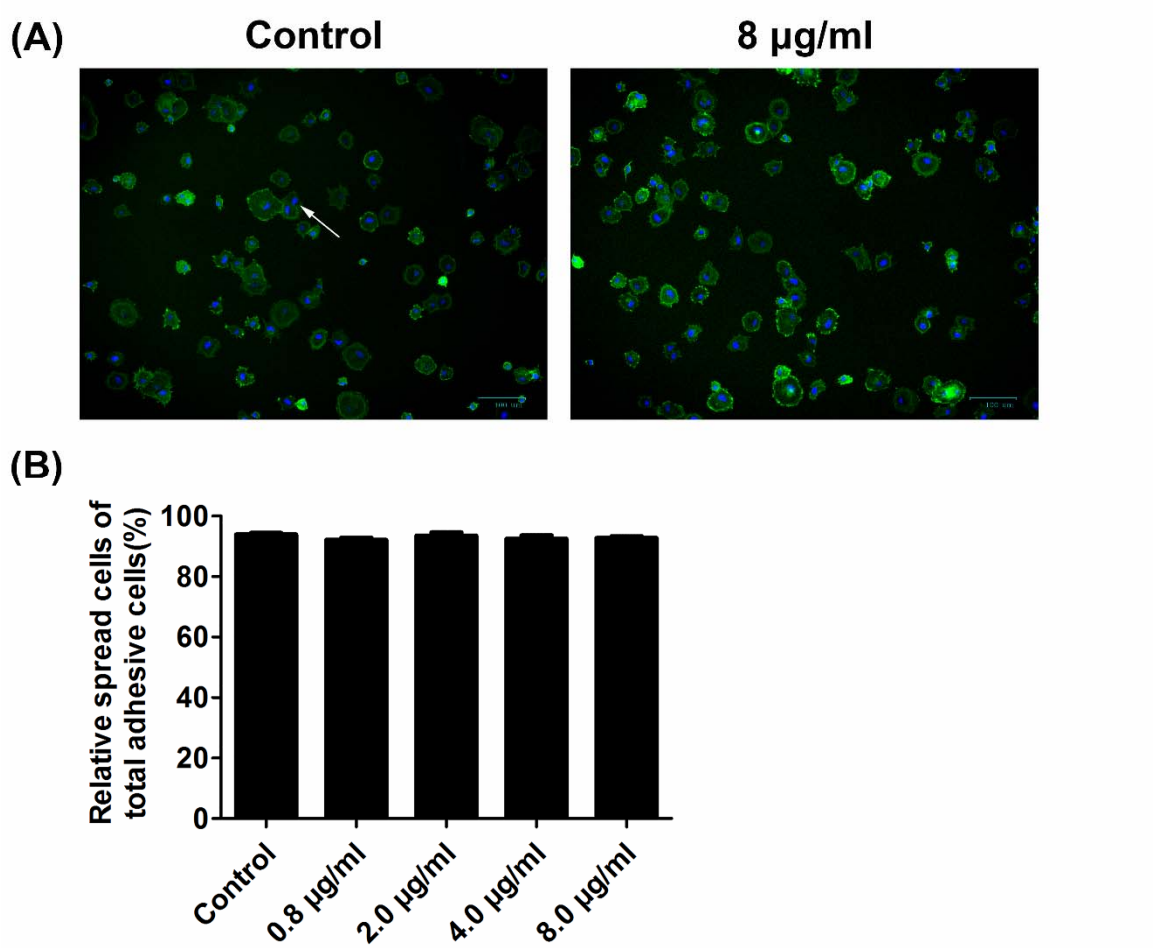

Figure 4. Effects of Celecoxib on cell spreading of skeletal muscle cells.

Skeletal muscle cells were treated with 0.8 μg/ml, 2 μg/ml, 4 μg/ml, and 8 μg/ml celecoxib for 24 hours. After plating for 30 minutes, the attached skeletal muscle cells started to spread out and were observed via F-actin staining. The spread cells were indicated by the white arrows. F-actin was stained green and nuclei were stained blue (A). The percentage of spreading cells out of adhered cells was shown in (B), and the data represented the mean ±SEM of three independent experiments. Scale bars, 100 μm.

DISCUSSION

The migration of satellite cells is important for muscle regeneration and healing. After muscle fibers are injured, regeneration relies mainly on its resident muscle satellite cells.[20,21] When inflammation processes are activated, circulating neutrophil is first recruited to the damage site,[24] followed by monocytes, which are converted into macrophages when reaching muscle tissue.[25] Macrophages facilitate the proliferation of satellite cells.[22,26,27] Both the neighboring satellite cells and every satellite cell along the same myofiber migrate to the lesion site, fusing with the injured fiber to repopulate the lost nuclei.[21] Satellite cells may migrate for a long distance to the lesion site.[26,28] Satellite cells are also important in regulating the activity of fibroblasts, which are crucial for extracellular matrix (ECM) synthesis and remodeling.[23] A recent study showed that ibuprofen impeded migration of skeletal muscle cells and the underlying molecular mechanism was to downregulate protein expressions of p130cas and CrkII, indicating a negative effect of traditional NSAIDs for muscle regeneration.[15] Our previous data showed that celecoxib had

no effect on protein expression of p130cas in skeletal muscle cells (data not shown). Therefore, our result did not reveal that celecoxib had any impact on cell migration. The difference between the effects of ibuprofen and celecoxib on protein expression of p130cas may account for the different effect on cell migration between ibuprofen and celecoxib.

Cell spreading is one of the crucial steps in cell migration. Cell spreads by the membrane protrusions at the leading edge of cells, known as lamellipodia.[29] Focal attachments of the edge and traction force make the cell body move forward.[30] Traditional NSAIDs were reported to restrain cell spreading of endothelial cells in human umbilical vein and rat ' s Achilles tendon cells.[31,32] A recent study also demonstrated ibuprofen, a traditional non-selective NSAID may impair the spreading and migration of skeletal muscle cells by downregulating protein expression.[15] Our results showed that celecoxib does not decrease skeletal muscle cell spreading in different doses, which may indicate there is less influence of COX-2 inhibitor on muscle migration that is important for the muscle regeneration.

The maximum observed plasma concentrations of the commercial formulation of celecoxib 400mg oral capsules was reported to be 611 ng/ml.[33] And the lowest concentration of celecoxib used in our studies was found at a level of 0.8μg/ml, which was even higher than the peak plasma concentration after oral administration of 400mg celecoxib. Celecoxib does not inhibit migration, proliferation, and spreading of skeletal muscle cells even in the higher concentration than that of the general doses of oral intake. These results demonstrated that oral administration of celecoxib, a COX-2 inhibitor for anti-inflammation might has less impact on the subsequent muscle recovery process.

The impairment to the muscle healing process caused by NSAIDs has become a major concern recently. The newest acronyms “PEACE (protect, elevate, avoid anti-inflammatory modalities, compress, educate) and LOVE (load, optimism, vascularisation, exercise)” guideline for treatments to immediate soft tissue injury in 2019 emphasize the avoidance of anti-inflammatory modalities for the concerning about this negative effect. Thus, NSAIDs was suggested to be abandoned in the standard care of muscle injuries.[10] However, an estimated 70 million prescriptions for NSAIDs annually in America were reported.[34] The use of analgesic drugs is very common in all elite sports player, amateur, and student-athletes.[35,36] Over 50% of FIFA World Cup players took NSAIDs at least once during the tournament.[37] Another report showed 75% of the student players had NSAIDs in the past 3 months before the survey, and 15% of them were daily users.[36] Despite the newest “PEACE and LOVE” guideline, the prescription and consumption of NSAIDs by doctors and players are still in a trend for different inevitable purposes. Our study attempted to add further information to the guideline that if it is imperative to use NSAIDs in some situation after the muscle injury, COX-2 inhibitor such as celecoxib might be the better choice for their less impact on the muscle recovery process.

There are limitations to this study. First, the results of this in vitro study may not be able to apply directly to human. Further in vivo studies or even human clinical trials should be done to validate the findings of this study. Second, the effect of celecoxib on myogenic differentiation of skeletal muscle cells needs also to be investigated for better understanding the role that celecoxib plays in treating injured muscle.

CONCLUSION

In conclusion, celecoxib does not inhibit migration, proliferation, and spreading of skeletal muscle cells. It might be an option for acute injury of muscles.

ABBREVIATIONS

NSAIDs: Nonsteroidal anti-inflammatory drugs; MTT: 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide.

ACKNOWLEDGEMENTS

We would like to thank Chang Gung Memorial Hospital, Taiwan for financially supporting this research (Grant No. CMRPG5I0031).

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希樂葆不影響骨骼肌細胞增生、移行及 F-actin 組成

陳航民 [1]　陳志嘉 [2]　林莉萍 [1,3]　蔡文鐘 [2,4]　蘇中慧 [1,3]

林口長庚紀念醫院 復健部 [1]
桃園長庚紀念醫院 復健科 [2]
長庚大學 臨床醫學研究所 [3]
長庚大學醫學院 醫學系 [4]

肌肉損傷為最常見的運動傷害之一，非固醇類抗發炎藥常用於肌肉損傷之治療，但 2019 年英國運動醫學期刊最新運動傷害處理原則(PEACE & LOVE)指出急性傷害期避免過度使用抗發炎藥，以免影響組織癒合。過去文獻指出非固醇類抗發炎藥會抑制肌肉細胞移行能力，此機制為肌肉癒合之關鍵。本研究目的為測試 COX-2 抑制劑希樂葆是否會影響肌肉細胞增生及移行能力。以 MTT 試驗檢測細胞增生能力，以體外傷口癒合試驗及細胞遷移實驗驗證細胞移行能力，以 F-actin 染色觀察細胞擴展能力。研究結果顯示希樂葆不會影響細胞增生及體外傷口癒合能力，此外希樂葆也不會影響細胞移行及擴展能力。儘管最新運動傷害處理原則(PEACE & LOVE)不建議使用抗發炎藥，但在不可避免的情況下，COX-2 抑制劑希樂葆與其他抗發炎藥相比可能是更好的選擇。（台灣復健醫誌 2021；49(2)：183 - 192）

關鍵詞：希樂葆(Celecoxib)，骨骼肌細胞(skeletal muscle cells)

通訊作者：蘇中慧教授，長庚大學臨床醫學研究所，333 桃園市龜山區文化一路 259 號。
電話：(03) 2118800 轉 3482　E-mail：jonghwei@mail.cgu.edu.tw
doi: 10.6315/TJPMR.202112_49(2).0005