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Percutaneous soft tissue release performed using a blunt cannula in rabbits with chronic collagenase-induced Achilles tendinopathy

Yueh-Ling Hsieh[a,*], Ming-Ta Lin[b], Chang-Zern Hong[c], Hsin-Shui Chen[d,e,**]

[a] Department of Physical Therapy, Graduate Institute of Rehabilitation Science, China Medical University, Taichung 40402, Taiwan
[b] Kuan-Ta Rehabilitation and Pain Clinic, Taichung 40652, Taiwan
[c] Taiwan Myopain Society, Taichung 40402, Taiwan
[d] Department of Physical Medicine and Rehabilitation, China Medical University, Bei-Gang Hospital, Yun-Lin 65152, Taiwan
[e] Department of Rehabilitation Medicine, School of Medicine, College of Medicine, China Medical University, Taichung 40402, Taiwan

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ABSTRACT

Background: This study investigated the effects of percutaneous soft tissue release (PSTR) performed using a blunt cannula on (1) the inflammatory cells-count, (2) expressions of calcitonin gene-related peptide (CGRP) and (3) substance P (SP) in rabbits with chronic phase of collagenase-induced Achilles tendinopathy.
Methods: Thirty-two adult male New Zealand rabbits were randomly divided into four groups: (1) collagenase and PSTR treatment; (2) collagenase and sham-operated PSTR treatment; (3) vehicle-only injection and PSTR treatment; and (4) vehicle-only injection and sham-operated PSTR treatment. Achilles tendon of adult male rabbits was injected with 10 μl of collagenase under ultrasonography localization. After 30 days, PSTR was performed using an 18G beauty cosmetic blunt tip micro cannula needle to release the soft tissue and paratenon above the inflamed Achilles tendon. The treated tendons and spinal cords of L5-S2 were harvested 5 days after treatment for histological assessment and immunohistochemical analysis.
Results: Histopathological examination revealed that PSTR achieved significant reduction in hypercellularity with pronounced infiltration of immune cells at the site of paratenon in tendons injected with collagenase compared with sham operation ($p < 0.05$). Immunohistochemical analysis also showed marked decrease in expression of CGRP in tendon and SP in dorsal horns after PSTR ($p < 0.05$).
Conclusions: This study showed positive effects in an animal model of chronic tendinopathy, and can be considered a treatment option, but that further research is necessary to determine its role in clinical practice.

1. Introduction

Achilles tendinopathy is a chronic degenerative and inflammatory condition characterized by repetitive activity-related pain and focal tendon tenderness. It afflicts and affects more those who regularly participate in recreational and competitive sports [1]. Numerous pharmacological treatments, such as nonsteroidal anti-inflammatory medications, and corticosteroid injections have been proposed to promote healing of this injury; however, in recalcitrant cases, the condition remains a source of frustration [2]. Hence, to explore nonpharmacological alternatives for modulating inflammatory responses with less adverse effects is of need.

Current understanding of the mechanisms involved in tendon injury and pain generation is limited. On histopathological examination, tendinopathy can be divided into peritendinitis and tendinosis (tendon degeneration), which can coexist [3]. Interventions have aimed at possible pain generators either within the Achilles tendon itself or its paratenon [4,5], with varying success. The paratenon can be involved in tendinopathy, and may present as “peritendinitis crepitans” due to adhesion between the tendon and the paratenon [6].

Percutaneous soft tissue release (PSTR) used for the release of adhesive soft tissues between the tendon sheath and the periosteum has shown promise in the treatment of trigger finger [7], contracture of quadriceps tendon [8] and lateral epicondylitis [9]. Nevertheless, it was only very recently that similar treatments have been tried in the Achilles tendon. Interventions involving large volumes of injectant [5] or minimally invasive surgical

* Corresponding author.
** Corresponding author at: Department of Physical Medicine and Rehabilitation, China Medical University, Bei-Gang Hospital, Yun-Lin 65152, Taiwan.
E-mail addresses: sherrie@mail.cmu.edu.tw (Y.-L. Hsieh), d0625@mail.bh.cmu.edu.tw (H.-S. Chen).

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techniques with a sharp surgical knife [4,10] or a needle with sharp cut edge [11] have been used for this procedure which, theoretically, increases the risk of tendon damage [12]. Application of PSTR to tendinopathic tissues using a blunt cannula has not been reported previously.

To avoid excessive tissue damage and bleeding, a new technique using a cosmetic blunt needle to release adhesive soft tissues has been developed [9]. This technique providing successful relief of pain in patients with chronic recurrent myofascial pain associated with lateral epicondylitis [9] and subtrochanteric bursitis [13] is much less invasive compared with the surgical techniques or percutaneous needle release reported previously.

Collagenase is known to have both proinflammatory and degenerative properties and it has previously been employed to induce tendinopathy in animal models [14]. Increased expression of calcitonin gene-related peptide (CGRP) in the sensory nerve endings and tenocytes has been reported in collagenase-induced tendon of animal models [15]. Substance P (SP) usually found in the brain and spinal cord is associated with inflammatory processes and pain [16]. These reported evidences suggested that CGRP and SP might have roles in the injured status and origin of pain in animals having chronic tendinopathy. This study evaluated the effects of PSTR performed using a blunt cannula in a rabbit model of chronic tendinopathy induced by injection of collagenase on the changes in CGRP expressions and inflammatory cells in the inflamed tendon, as well as SP in spinal dorsal horns.

2. Materials and methods

2.1. General design

All animal experiments followed the procedures approved by the Animal Care and Use Committee of China Medical University (NO: 102-26-N) in accordance with the National Institutes of Health 'Guide for the Care and Use of Laboratory Animals'. Thirty-two animals were randomly divided into four groups: (1) collagenase and PSTR treatment (n = 8, Col-PSTR); (2) collagenase and sham-operated PSTR treatment (n = 8, Col-sPSTR); (3) vehicle-only injection and PSTR treatment (n = 8, Veh-PSTR); and (4) vehicle-only injection and sham-operated PSTR treatment (n = 8, Veh-sPSTR). PSTR treatment or sham operation was started 30 days after collagenase/vehicle administration for one session. Five day after the treatment of one-session PSTR, the animals were sacrificed for histopathology and immunoassays. All assessments were performed by a laboratory technician and a pathologist blinded to the group assignment.

2.2. Animal preparation

Adult male New Zealand rabbits (age, 16–20 weeks; body weight, 2.5–3.0 kg; Lin's Ranch, Taiwan) were maintained in the animal facility under an artificial 12-h light-dark cycle. The animals were fed commercial rabbit chow and water ad libitum. Adequate injection and anesthesia were planned in order to minimize the levels of pain and discomfort according to the ethical guidelines of the International Association for Study of Pain in animals [17]. Effort was made to minimize discomfort and to reduce the number of animals used. All animal experiments were conducted following the procedure approved by the Animal Care and Use Committee of China Medical University in accordance with the Guidelines for Animal Experimentation (No. 102-26-N).

2.3. Collagenase-induced tendinopathy

The rabbits were briefly anesthetized with 4% isoflurane (AERRANE, Baxer Healthcare Corporation, Puerto Rico). The needle tip was localized to the center of the tendon under ultrasound guidance (Terason t3000^{TM} Ultrasound System, Massachusetts, USA). Then ten microliters (10 mg/ml in 0.9% saline) of collagenase I (Sigma–Aldrich, Missouri, USA) was injected into the medial gastrocnemius part of the Achilles tendon, 0.4 cm above the calcaneal tuberosity of the randomly selected unilateral limb of each rabbits, while the contralateral limb received no injection.

2.4. Percutaneous soft tissue release

Percutaneous soft tissue release was performed with a disposable 18G beauty cosmetic blunt tip micro cannula needle (70 mm in length, Lot. 010798, Peiseux-Le-Hauberger, France) 30 days after injection of collagenase, following a procedure used previously [9]. Under anesthesia, the skin was penetrated with an 18G injection needle to make a hole for the penetration of this blunt cannula. The cannula was inserted into the hole to reach the subcutaneous tissue layer, and moved slowly toward the tendinopathy region above the calcaneal tuberosity. Forward and backward movements were then repeatedly performed to release the soft tissues and paratenon above the Achilles tendon. With resistance of needle movement reduced, the needle was pulled back to the subcutaneous layer, and then turned to a different direction for a new track of penetration. Finally, this cannula could sweep around the calcaneal tuberosity area freely with no resistance. For sham-operated PSTR, the needle was inserted into the subcutaneous layer of the Achilles tendon at a depth approximately 1–2 mm from the skin surface. The needle was placed without penetrating the paratenon tissues and remained in place for the same duration as with PSTR treatment.

2.5. Histological and immunohistochemical examinations

The harvested Achilles tendons and spinal cords of L5-S2 were fixed in a 4% buffered paraformaldehyde solution for 1 week. After fixation, they were embedded in paraffin. The tendons and spinal cords were sectioned and prepared for hematoxylin and eosin (HE) staining, CGRP and SP immunohistochemistry to assess the inflammatory and nociceptive responses. Analyses was performed on 10 alternate sections per rabbit, selected using a systematic-random series with a random start. Sections were stained with polyclonal goat CGRP, (diluted 1:250, ab36001, Abcam, USA) and mouse polyclonal SP (diluted 1:2000, ab14184, Abcam, USA), followed by a biotinylated anti-mouse (sc-3697) or anti-goat (sc-3851) immunoglobulins (Santa Cruz Biotechnology) and incubated with 3,3′-diaminobenzidine (TA-060-QHDX, Thermo Fisher Scientific Inc., UK), dehydrated and cover-slipped with Permount (Sigma, New Jersey, USA). Negative controls were performed by substituting the primary antibody with non-immune serum. The percentage of the ratio of strong positive pixels to total counter-stained pixels allowed quantification of SP- and CGRP-like immunoreactivities (SP-IR and CGRP-IR). All histological and immunoreactive studies were assessed by a pathologist blinded to the group assignment.

2.6. Image quantification and statistical analysis

Three randomly selected fields of the tendon and superficial dorsal horn were examined and photographed using a light microscope (BX43, Olympus America Inc, New York, USA) and a cooled digital color camera with a resolution of 1360 × 1024 pixels (DP70, Olympus America Inc). The digital images were analyzed using computer-based morphometry (Image-Pro® Plus 4.5 software, Media Cybernetics, Silver Spring, Maryland, USA). Data were expressed as mean ± standard deviation (SD). The various outcome parameters were assessed using one-way analysis of variance

(ANOVA) and Scheffe's method. A p value of <0.05 was considered statistically significant. All data were analyzed using Statistical Package for Social Science (SPSS) version 20.0 for Windows (IBM Corp, Armonk, New York, USA).

3. Results

3.1. Effects of PSTR on inflammatory cells

Results of HE study showed high cellularity with pronounced infiltration of immune cells at the site of paratenon in rabbit's Achilles injected with collagenase as compared with those treated with vehicle (Fig. 1). The percentage of cellularity was significantly decreased, showing less inflammation and cell infiltration in Col-PSTR groups when compared with Col-sPSTR group ($p < 0.05$). No significant difference in cellularity was found between Veh-PSTR and Veh-sPSTR groups ($p > 0.05$, Fig. 1E).

3.2. Effects of PSTR on CGRP-like immunoreactivity of tendon

Immunohistochemical staining showed CGRP stained brown in high-cellularity areas. CGRP-IR expression in collagenase-treated tendons were significantly increased compared with that in vehicle-treated tendons (Fig. 2,$p < 0.05$). After collagenase-induced tendinopathy, CGRP-IR was significantly decreased in Col-PSTR groups when compared with that in the Col-sPSTR group ($p < 0.05$). No significant difference in CGRP-IR was found between Veh-PSTR and Veh-sPSTR groups ($p > 0.05$, Fig. 2E).

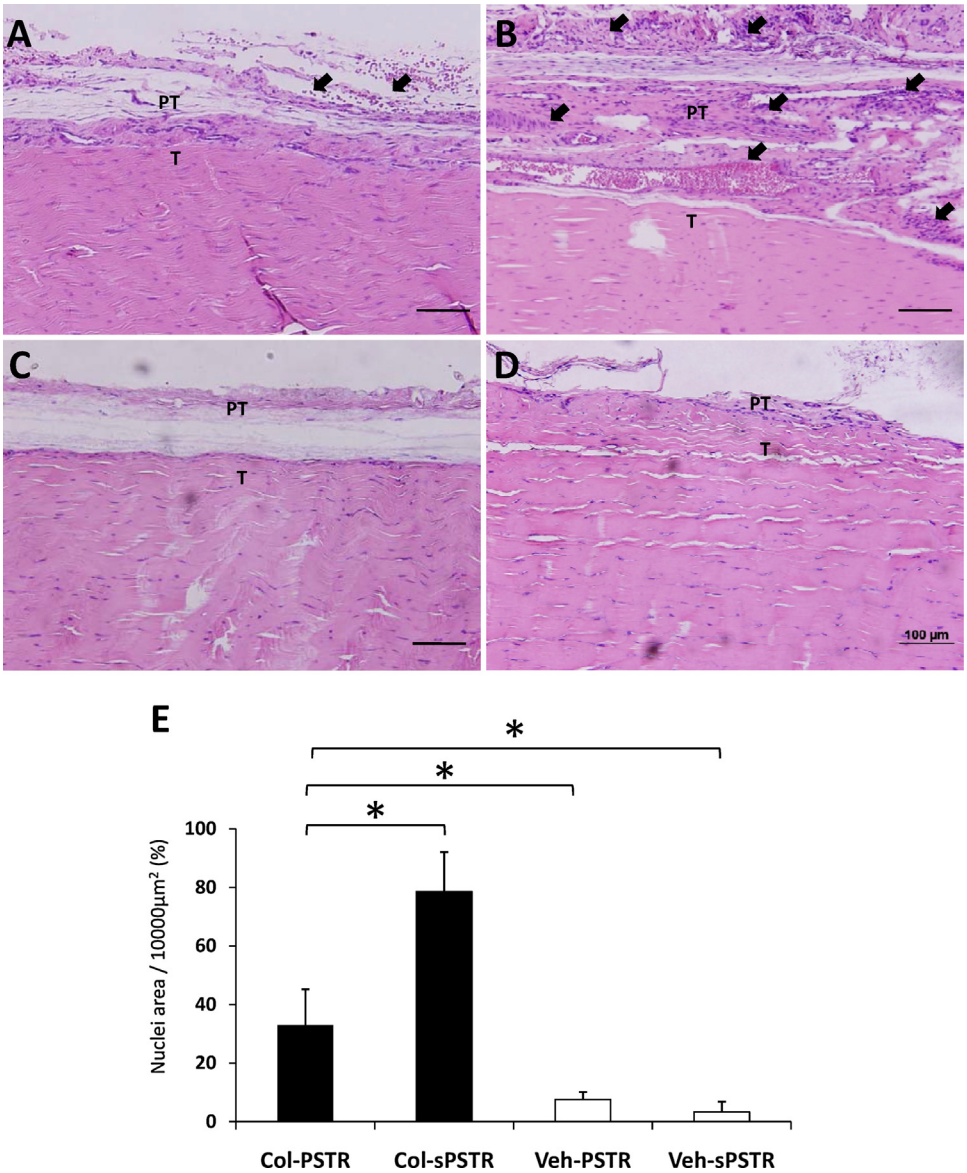

Fig. 1. Photomicrographs of Achilles tendon samples with collagenase-induced tendinopathy treated using percutaneous soft tissue release (Col-PSTR group) and sham operation (Col-sPSTR group), as well as its controls, vehicle injection treated with PSTR (Veh-PSTR group) and sPSTR (Veh-sPSTR group). In rabbits from the Col-PSTR group, less infiltration and less accumulation of inflammatory cells was observed (A) when compared with rabbits from the Col-sPSTR group with an even greater and massive inflammatory cell infiltration observed in the paratenon (PT) area (B). However, in rabbits from the Veh-PSTR and Veh-sPSTR groups, the tendon (T) tissues show normal histological appearance (C and D). The quantitative analysis of H&E for inflamed cells is shown as E. * indicates statistically significant difference ($p < 0.05$) when the data of the Col-PSTR group were compared with those of Col-sPSTR, Veh-PSTR and Veh-sPSTR groups. Arrowheads indicate increased cellularity, hypertrophied paratenon and inflammatory cells after collagenase induction. Bar = 100 μm.

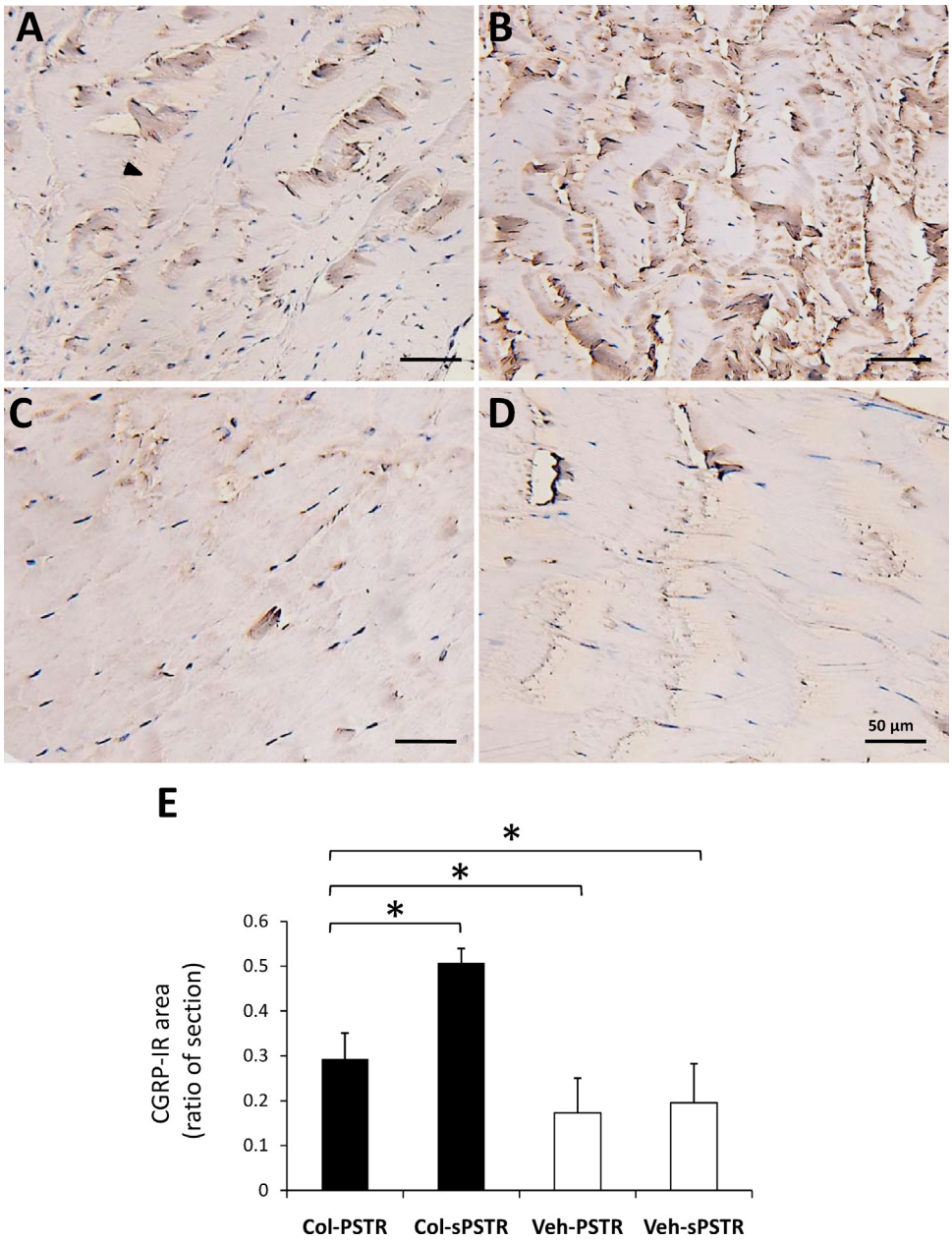

Fig. 2. Photomicrographs showing the immunohistochemical staining of calcitonin gene-related peptide (CGRP) in collagenase-induced tendinopathy treated using percutaneous soft tissue release (Col-PSTR, A) and sham operation (Col-sPSTR group, B), as well as its controls, vehicle injection treated with PSTR (Veh-PSTR group, C) and sPSTR (Veh-sPSTR group, D). The quantitative analysis of CGRP-like immunoreactivity (CGRP-IR) area is shown as E. * indicates statistically significant difference ($p < 0.05$) when the data of the Col-PSTR group were compared with those of Col-sPSTR, Veh-PSTR and Veh-sPSTR groups. Bar = 50 μm.

3.3. Effects of PSTR on SP-like immunoreactivity of spinal dorsal horns

The patterns of SP-IR in L5-S2 segments for the four experimental groups are presented in Fig. 3, indicating significant differences ($p < 0.05$). In animals of the vehicle-treated controls, SP-IR was sparely expressed in the nuclei of cells of the superficial laminaes in L5-S2 dorsal horn spinal cords which showed no statistically significant differences between Veh-PSTR and Veh-sPSTR groups ($p > 0.05$). The nuclei of SP-IR neurons were visualized as brown precipitates and some cytoplasmic staining was seen distributed in the bilateral superficial laminaes (I–II) of the dorsal horn in collagenase-treated groups. Significant reduction in the SP-IR value was found in bilateral superficial laminaes in Col-PSTR groups when compared with those in the Col-sPSTR group ($p < 0.05$, Fig. 3E).

4. Discussion

The characterization of chronic tendinopathy model with collagenase-induced inflammation used in this study revealed that pronounced infiltration of immune cells, hypertrophied paratenon, increased expression of CGRP in tendon and SP in spinal cord were still found at the site of paratenon injected with collagenase 30 days after induction. Therefore, use of this experimental model was suitable for studying the PSTR treatment effects on chronic inflammatory responses in tendon tissue. This finding agrees with other studies on tissue repair in the rabbit and with reports on the treatment of tendinopathy [14,18]. Moreover, this study also demonstrated the beneficial effects of PSTR in rabbits with Achilles tendinopathy at the chronic phase of collagenase-induced inflammation. To our knowledge, a study

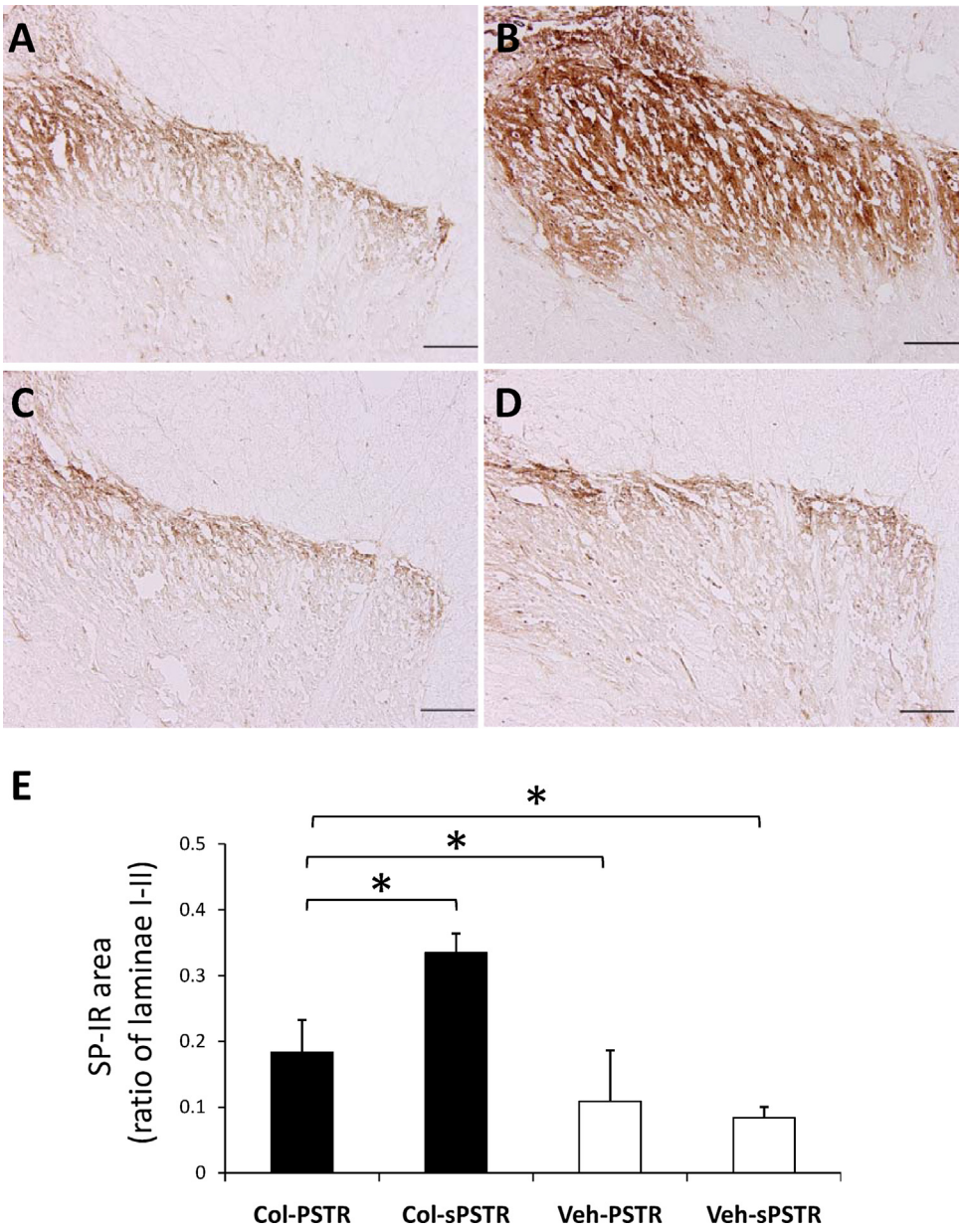

Fig. 3. Photomicrographs showing the immunohistochemical staining of substance P (SP) in spinal cords with collagenase-induced tendinopathy treated using percutaneous soft tissue release (Col-PSTR, A) and sham operation (Col-sPSTR group, B), as well as its controls, vehicle injection treated with PSTR (Veh-PSTR group, C) and sPSTR (Veh-sPSTR group, D). The quantitative analysis of SP-like immunoreactivity (SP-IR) area in laminaes I–II is shown as E. * indicates statistically significant difference ($p < 0.05$) when the data for the Col-PSTR group were compared with those of Col-sPSTR, Veh-PSTR and Veh-sPSTR groups. Bar = 50 μm.

applying PSTR to animal model-based tendinopathic tissues has not been previously reported.

Chronic Achilles tendinopathy usually has tight adhesions around the thickened paratenon (especially between the paratenon and the crural fascia) [19]. The ingrowths of sensory and sympathetic nerves from the paratenon with release of nociceptive substances may play an essential role in causing pain [19]. Most surgical procedures aim at debridement or tenotomy of the tendon itself which also included incision, release and removal of paratenon. Tendinopathy and paratendinopathy often coexist. It is therefore uncertain which part of the procedure is responsible for a possible favorable outcome. Some procedures that address only peritendineous structures, such as in open or minimally invasive paratenectomy [20], percutaneous tenotomy and Achilles tendoscopy where the paratenon is released, can also relieve symptoms [21]. However, with surgery of the tendon proper, including minimally invasive tenotomy, the tendon is still temporarily weakened and needs a long time for recovery [20]. Therefore, denervating the Achilles tendon by release of the paratenon is sufficient to cause pain relief in the majority of patients. This type of treatment has the additional advantage of a shorter recovery time when compared with treatment options that address the tendon itself [19]. The percutaneous technique may provide a lower complication rate than the open or arthroscopic debridement of the damaged portion of the tendon with repair, lengthening, or pathologic release of the remaining healthy tendon [14].

The PSTR procedure used in this study is actually similar to that of percutaneous release of adhesion performed previously by orthopedic surgeon with a knife or a 18G needle [22]. The major difference is the use of a blunt cannula instead of a sharp knife or needle for PSTR. Prior research demonstrated that the recovery

period can be much shortened and the patient with lateral epicondylitis has less suffering after PSTR [9]. This study targeted the dual generators of pain by PSTR as a novel treatment for chronic Achilles tendinopathy. The present results demonstrated significant decrease in both infiltration of inflamed cells and release of CGRP in paratenon and tendon after PSTR in rabbits with collagenase-induced Achilles tendinopathy.

The localization of CGRP-containing axons may mediate neurogenic inflammation and pain perception [23]. CGRP might also be involved in the pathogenesis and origin of pain of tendinopathy [15]. A study demonstrated markedly decreased CGRP-IR in collagenase-induced Achilles tendon after a microtenotomy using radiofrequency [24]. The release of SP in superficial laminae of the spinal dorsal horn is involved in transmission of noxious stimuli [25]. Furthermore, SP is an important mediator involved in nociceptor sensitization, hyperalgesia, and allodynia following tissue injury [26]. An increase in spinal SP concentration was also found in collagenase-injected animals, as well as an increase in CGRP concentration in tendon [27]. The present results showed increased expression profiles of SP and CGRP in dorsal horns and tendon presumably reflecting similar inflammatory actions in a collagenase-induced chronic tendinopathy model, which were consistent with previous findings [27]. PSTR reducing the overexpression of CGRP in tendon and SP in dorsal horns may relieve pain by lowering the potential for local inflammation and tissue adhesion and provide therapeutic effects on reduction of inflammatory response.

Different stages of Achilles tendon lesions may differ in their response to a specific operative technique. However, surgical decompression of the tendon is often associated with a high complication rate of wound-healing problems [28]. Minimally invasive procedures may result in lower complication rates compared with open surgical procedures [29]. Most minimally invasive techniques focus mainly on the peritendineous tissues and intend to eliminate neovascularization with its accompanying nerves as a cause of pain and disease progression [20]. In addition, it was shown that the minimally invasive paratenon debridement with higher patient satisfaction and lower complication rates is superior to percutaneous longitudinal tenotomy [30]. PSTR is a fashion of dry needling which involves inserting a blunt needle into a lesion of interest in subcutaneous tissue with repeated puncture. Paratenon needling using PSTR is thought to reduce an inflammatory response by decreasing infiltration of inflammatory cells leading to granulation tissue formation. Additionally, release of nociceptive substances, CGRP and SP, from sensory and sympathetic nerves in the paratenon and spinal cords was also reduced after PSTR in this chronic tendinopathy model. The evidence suggests that paratenon needling with PSTR improves nociception and inflammation in animals with chronic tendinopathy.

This current study had several limitations. Although validated, the collagenase-induced tendinopathy model may not truly represent an *in vivo* chronic tendinopathy and there are several other mechanically induced tendinopathy models available. However, all such models have limitations. Secondly, this study lacks a functional examination and a follow-up time frame after treatment to demonstrate a full restoration of the tendon, which will be the subject of future, longer-term studies, and to investigate the effect in different models of tendinopathy.

5. Conclusion

PSTR performed using a blunt cannula improved histological appearance, inflammation and nociception at chronic phase of collagenase-induced tendinopathy, demonstrating evidence basis as a minimally invasive treatment. It showed positive effects in an animal model of chronic tendinopathy, and can be considered a treatment option, but that further research is necessary to determine its role in clinical practice.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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