SCIENTIFIC ARTICLE

The Effects of Locally Injected Triamcinolone on Entrapment Neuropathy in a Rat Chronic Constriction Injury Model

Masataka Shibayama, MD, Kazuki Kuniyoshi, MD, Takane Suzuki, MD, Kazuyo Yamauchi, MD, Seiji Ohtori, MD, Kazuhisa Takahashi, MD

Purpose Patients with idiopathic carpal tunnel syndrome are commonly treated by steroid injections into the carpal tunnel. We administered triamcinolone (Tr) to chronic constriction injury model rats. We hypothesized that Tr administration would have both favorable behavioral effects and quantifiable immunohistological effects on compressed nerves.

Methods Thirty-six male Wister rats were used. For rats to be treated with Tr, we loosely ligated their right sciatic nerves at 4 sites. Sham rats had their nerves exposed without ligation. On postoperative day 7, we reexposed their ligated nerves, after which we delivered either 0.1 mg of Tr (0.1-mg group), 0.5 mg of Tr (0.5-mg group), or normal saline (saline group) around the nerve fibers at the injured sites. Gait was analyzed, and allodynia was assessed with von Frey hairs, before surgery and on postoperative days 3, 7, 10, 14, and 21. The right sciatic nerve was resected and stained using hematoxylin-eosin, and the fourth and fifth lumbar dorsal root ganglia (DRG) were removed and assessed by immunohistochemistry for calcitonin gene-related peptide (CGRP) and activating transcription factor 3 (ATF3) on postoperative day 21. In addition, interleukin-1β (IL-1β) in sciatic nerve was quantified using enzyme-linked immunosorbent assays.

Results Mechanical allodynia was significantly decreased in the 0.5-mg group compared with the saline group. In hematoxylin-eosin sections, the extent of inflammation-induced edema between the nerve fibers and infiltration of inflammatory cells was significantly reduced in the 0.5-mg group compared with the saline group. IL-1β levels at the sciatic nerve in the 0.5-mg group were significantly lower than those in the saline group.

Conclusions Tr-treated chronic constriction injury rats exhibited significant alleviation of sensory disturbance, edema, inflammation, and pain-related peptide upregulation. These phenomena suggest the validity of Tr administration as a treatment affecting the nerve itself. *(J Hand Surg Am. 2014;39(9):1714–1721.*

Type of study/level of evidence Therapeutic I.

Key words Carpal tunnel syndrome, chronic constriction injury model, interleukin 1-beta, pain, triamcinolone.

THE PATHOPHYSIOLOGY OF CARPAL tunnel syndrome (CTS) is multifactorial. Increased pressure in the carpal canal plays a key role in its development. Although the precise etiology of increased carpal tunnel pressure in CTS is uncertain, experimental evidence suggests that compression or

From the Department of Orthopedic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan.

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Corresponding author: Masataka Shibayama, MD, Department of Orthopedic Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan; e-mail: aohigesensei@yahoo.co.jp.

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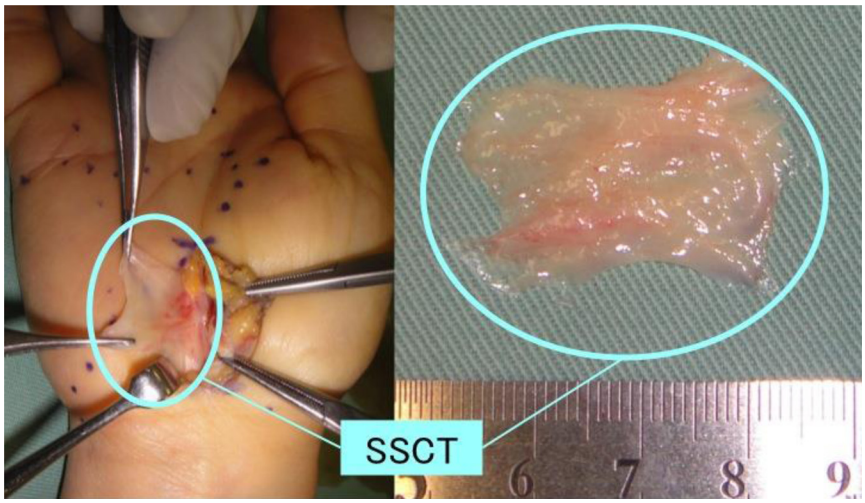

FIGURE 1: SSCT is the rough connective tissue between the median nerve and the flexor tendons.

inflammation is causative. Increased pressure in the carpal tunnel can injure the nerve directly, impair axonal transport, or compress vessels in the perineurium and cause nerve ischemia. The subsynovial connective tissue (SSCT) serves as a sliding unit to reduce the friction and to protect the blood supply to the tendon and synovium[1,2] (Fig. 1), and histological and biological changes have been noted within the SSCT of patients with CTS. Several investigators have suggested that the nerve compression may actually be secondary to an initial change in SSCT stiffness, volume, or permeability.[3,4]

Several options are available for the treatment of patients with CTS, and the modality chosen depends on the severity of nerve dysfunction (mild, moderate, and severe). For patients with mild-to-moderate CTS, conservative therapy is generally considered to be a reasonable first option, with successful outcomes in the range of 20% to 93%.[5,6] Conservative treatment includes oral medications, wrist orthosis fabrication, and local injections. Since Phalen and Kendrick reported steroid injections into the carpal tunnel in 1957,[7] the clinical effectiveness of this method has been reported by many researchers.[8,9] However, the role of steroid injections and their mechanism of action has been controversial. In general, injections are directed at the median nerve or the SSCT. In this study, we focused on the effects of steroid injection on the nerve. Although there has been some basic research on steroid injection about the nerve,[10–12] few studies have reported direct administration of steroids on the damaged part of a nerve fiber.[13]

The actions of several major proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 are also associated with pain, hypersensitivity, and perhaps, neuropathic pain.[14–16] However, accumulating evidence implicates the direct involvement of IL-1β in the persistent increase in sensory neuron excitability commonly observed after a peripheral nerve injury, such as chronic constriction injury (CCI) in rats.[17] For instance, the messenger ribonucleic acid and protein expression of IL-1β receptor type 1 in sensory neurons implies that IL-1β can directly affect primary afferents.[18–20] In agreement with this finding, the electrical properties of sensory neurons show changes consistent with increased excitability within minutes of IL-1β application in addition to the onset of pain-related behaviors after intraplantar injections of IL-1β.[20,21] Also IL-1β expression, secretion, and processing are upregulated for several days after a peripheral nerve injury, and 5- to 6-day exposure to IL-1β alters the excitability of dorsal root ganglion (DRG) neurons.[22–25] Moreover, the rat CCI model has shown mechanical allodynia and increased calcitonin gene-related peptide (CGRP) and activating transcription factor 3 (ATF3) expression in DRG neurons.[26,27] We therefore investigated IL-1β changes in injured nerve fibers and the expression of CGRP and ATF3 in DRG neurons in this study.

The purpose of the current study was to conduct behavioral, immunohistochemical, and biochemical evaluations of the direct effect of triamcinolone acetonide (Tr) on the nerve in the rat CCI model.

MATERIALS AND METHODS

Ethics statement

All protocols for animal procedures were approved by the ethics committee of our institution and were in accordance with the National Institutes of Health