REVIEW ARTICLE

Adv Psychiatry Neurol 2022; 31 (2): 85-94
DOI: https://doi.org/10.5114/ppn.2022.116880



Carpal tunnel syndrome conservative treatment: a literature review

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Submitted: 28.01.2022
Accepted: 15.03.2022

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Abstract

Purpose: Carpal tunnel syndrome (CTS) is the most common compression neuropathy, which is associated with a significant psychosocial and economic burden. In this paper, the literature on the current knowledge about the physiology and pathology of peripheral nerves during the course of CTS is reviewed, with a focus on currently used treatment options and the rationale for their use. Epidemiology, risk factors, etiology, clinical features and conservative treatment have been searched for, with all full-text, English language articles being included in the study. This paper aims to present the recent findings on CTS treatment while also suggesting a direction for further clinical trials.

Views: The search in PubMed and Google Scholar Databases revealed 229 articles of which 71 met the research criteria. The evidence regarding standard treatment methods of conservative CTS treatment is presented. CTS is a relatively common condition, which affects women more often than men. It is a multifactorial disease, and its clinical presentation mostly consists of symptoms distal to the entrapment site, including numbness, tingling, weakness and pain. Electrodiagnostic studies are considered to be the gold standard in CTS diagnosis. The conservative treatment methods reviewed are acupuncture, extracorporeal shock wave therapy, hydrodissection, kinesiotaping, corticosteroid injection, low level laser therapy, splints, platelet-rich plasma injection, manual therapy, ultrasound and phonophoresis.

Conclusions: Based on the current body of knowledge, we conclude that the conservative CTS treatment is very safe, but the effectiveness of reviewed methods differs. The first promising results presented by various studies motivate the need for further research on novel treatment methods.

Key words: physiotherapy, carpal tunnel syndrome, conservative treatment, peripheral nervous system.

INTRODUCTION

Carpal tunnel syndrome (CTS) is a common upper limb nerve entrapment syndrome which carries significant economic and social burden to the affected individuals. Its main feature is a reduction of the space inside the carpal tunnel thus interfering with the spatial relationship between its contents, causing symptoms distal to the lesion site. This paper aims to present the recent findings in the scope of CTS treatment, and propose a direction for further clinical trials.

METHOD AND RESULTS

PubMed was searched for articles published between January 1, 2016 and March 23, 2021 using the phrase "Carpal tunnel syndrome" as the MeSH phrase. The search result was filtered by selecting the conditions "meta-analysis", "systematic review", and "randomized controlled trial". We searched for epidemiology, risk factors, etiology, clinical features and treatment. All full-text, English language articles were included. Altogether 229 articles were identified, of which 72 were selected with the aim to give a comprehensive review of current CTS treatment methods.

EPIDEMIOLOGY

The annual incidence of CTS is ranging from 428 in women and 182 in men per 100,000 adults [1] with the prevalence of 3-5% in general population, raising up to 6% in women aged over 40 [2]. CTS severity may vary greatly between patients, from mild symptoms such as transient paresthesia or dysesthesia to nocturnal pain,

sleep disturbance, muscle weakness and constant pain. Electrodiagnostic studies are conducted to confirm the diagnosis, with ultrasound imaging adding value to electrodiagnostic tests [3]. Tensor diffusion magnetic resonance imaging (MRI) is also a valuable option for CTS diagnosis [4].

PATHOGENESIS

Studies have shown ischemia, edema, intraneural and extraneural fibrosis of the affected nerve in CTS [5]. A prolonged exposition to these factors changes axonal transport and consequently the excursion of the nerve may become impaired [6]; eventually demyelination and axon degeneration may occur. The entire process of demyelination alongside with changes in the quantity and regulation of ion channels is implicated with spontaneous ectopic generation of action potentials [7, 8]. These sites are called AIGS (abnormal impulse generating sites). Neuroinflammation can occur beyond the site of compression. It is also present in the spinal root ganglia and may explain why symptoms occur not only at the anatomical sites of nerve innervation but also in other areas innervated by the nerves originating from the same nerve root. The bilateral presentation of symptoms occurs in 60% [9] to 74% [10] patients with CTS, which may be caused by the inflammatory response of glial cells that can spread to the spinal cord and the contralateral dorsal root ganglion (DRG) [11]. This distant response may be associated with the changes present in the central nervous system observed in CTS [12]. In more severe cases of neuropathic pain, the extraterritorial spread of symptoms is more prevalent (Figure 1).

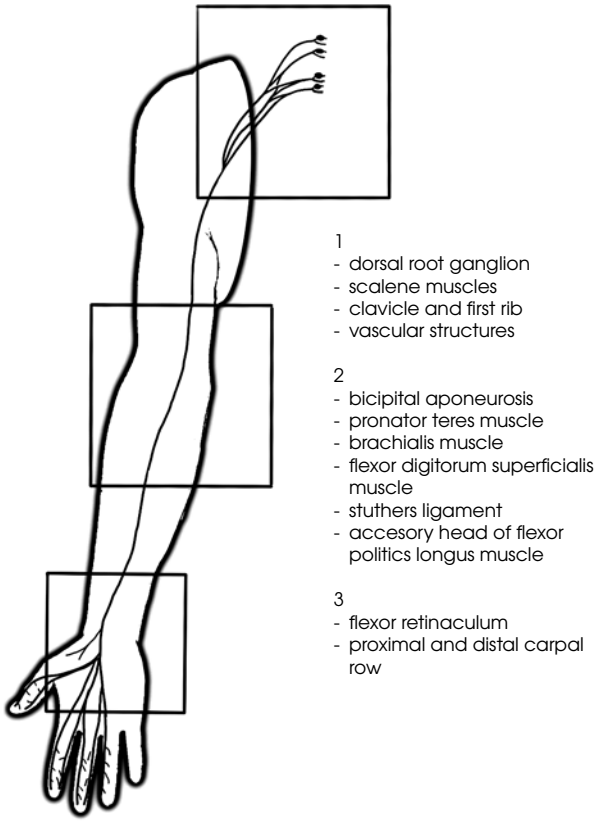


Figure 1. Possible anatomical contributions to carpal tunnel syndrome development

PHYSIOLOGY AND PATHOPHYSIOLOGY

Dorsal root ganglion

The dorsal root ganglion (DRG) is a crucial structure for sensory transduction and modulation, including pain transmission [13], because it houses the somata of the primary sensory neurons (PSNs). Each DRG consists of up to 15,000 PSNs cell bodies and approximately eight-fold more glial cells [14]. In contrast to peripheral nerves, the DRG are not provided with a blood-nerve barrier, which makes them prone to irritation by biochemical agents.

The connective tissue of the nerve

The endoneurium envelops a singular axon and provides it with constant endoneural environment and fluid pressure gradient. The perineurium envelops a few to a few hundred axons making a fascicle. The epineurium's main goals are to biomechanically protect the nerve from mechanical deformation due to compression or elongation, and allow for the gliding of the nerve trunk among the surrounding tissues and the gliding of fascicles inside the nerve trunk. The main goal of the mesoneurium is to provide enough mobility between the nerve trunk and the surrounding tissues. It also supports the extrinsic blood vessels and attaches the nerve trunk to the surrounding tissues.

Axonal transport

Axonal transport is an energy-dependent system that transports many necessary substances synthetized in the cell somata to the terminal parts of the axon (anterograde) and vice versa (retrograde). These substances include neurotransmitters and cytoskeleton components. The prolonged (eight hours) compression of just 20 mmHg can reduce fast anterograde axonal transport and two-hour compression of 30-50 mmHg effects in a block of axonal transport, which is reversible in 24 hours. In this case, two hours of 200 mmHg compression was reversible within three days [15]. Retrograde transport is also dose-dependent and can be blocked or limited via nerve compression from 20 mmHg [16].

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Blood supply

Each fascicle is segmentally supplied by branches from epineural vessels. Two diffusion barriers, i.e., blood-nerve barriers, are located in the perineurium and the endoneurium, providing a homeostatic endoneural environment for uninterrupted axonal transport and nerve impulse conduction. Damage to these barriers, e.g., mechanical compression, may cause intraneural pathophysiological changes and impair nerve function [17]. A nerve elongation of 8% results in a slowing of intraneural blood flow while 15% elongation causes complete arrest of intraneural blood flow. A return of blood flow is dependent on time and severity of hypoperfusion [18, 19].

Compression and elongation

Nerve conduction is limited by 70% in the case of one hour 6% elongation of the nerve while a complete conduction block occurs with a 12% one-hour elongation [20]. If the nerve is no longer elongated, then nerve conduction should return to normal but it is dependent on the dose of elongation [21]. Two-hour compression by pressures of 150 to 200 mmHg produces a transient increase in precursors to neuropeptide Y (CPON – C-terminal flanking peptide of neuropeptide Y) in DRGs. This supports the concept that local nerve compression activates the entire neuron [22]. Chronic compression results in the prominent upregulation of CPON and other neuropeptides [22, 23]. Intraneural structural changes, such as hypoperfusion and demyelination of the nerve, occur on the borders of compression similar to tourniquet compression.

Pressure gradient

The pressure gradient is the specific ratio of pressure between the tunnel of the nerve (PT), capillary pressure (PC), arterial pressure (PA), venous pressure (PV), and endoneural pressure (PF). According to Sunderland, the normal gradient is PA > PC > PF > PV > PT [24]. In the case of even mild compression of 20 mmHg, the intraneural pressure can rise due to impaired axonal transport and blood flow. In healthy people, the pressure inside the carpal tunnel is approximately 2.5 mmHg in the neutral position. It is 30-50 mmHg in the neutral position in CTS patients. This increases to 90-110 mmHg in wrist carpal and dorsal flexion and can reverse the pressure gradient. The nocturnal occurrence of symptoms, common in CTS, is associated with a lower blood pressure in arteries and veins because the tissue pressure for nerve fiber viability is 30 mmHg below the diastolic blood pressure.

Nerve innervation

Connective tissue of peripheral nerves is innervated by nervi nervorum. These thin, unmyelinated fibers terminate in free endings in the connective tissue of the nerve sheath. They have been shown to contain neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) [25]. These fibers respond to a nociceptive stimuli such as pressure applied on the nerve trunk, increased intrafascicular pressure, and increased tension. In the case of nerve trauma, the nervi nervorum can cause neurogenic inflammation due to release of CGRP and substance P.

RISK FACTORS

CTS is considered to be an idiopathic condition, however there are factors which increase the risk of its occurrence. These can be divided into four categories: extrinsic factors altering volume of tunnel contents, extrinsic factors altering the cross section of the tunnel, intrinsic factors and neuropathic factors [26] (Table 1).

CONSERVATIVE TREATMENT

Acupuncture and acupressure

Acupuncture and acupressure are the supportive therapies based on Chinese medicine. Acupuncture uses needles to alleviate symptoms while pressure is applied to the affected areas in acupressure, without the use of needles. Electroacupuncture uses electrical current that passes between two needles. PC7 or the Daling point is especially considered when managing CTS; it was found to cause an increase of endomorpin-1, beta-endorphin, serotonin, dopamine, and enkephalin levels in the brain tissues and plasma [27]. Acupressure was found to be more effective compared to the placebo and splints regarding the functional status and nerve conduction studies [28]; however, another study suggests that acu-

Table 1. Carpal tunnel syndrome risk factors

Extrinsic (volume)	Extrinsic (contour)	Intrinsic	Neuropathic
Pregnancy	Fractures of the distal radius	Tumor	Diabetes
Menopause	Fractures of the carpal bones	Ganglion cyst	Alcoholism
Obesity	Arthritis	Metastases	Vitamin deficiency
Kidney failure			Exposure to toxins
Hypothyroidism			

puncture with splinting does not produce better results than splinting alone [29] or has no effect compared to the placebo or sham intervention [30]. Acupuncture was shown to be more effective than ibuprofen in improving the functional status and better than splinting alone [31]; acupuncture with splint was found to be better than celebrex with splint in improving symptoms and distal motor latency [32]. The basic science of acupuncture is contrary to the Western medical knowledge as it is rooted in the traditional Chinese medicine. Further research should continue to develop our knowledge of the mechanisms of acupuncture treatment in relation to contemporary medical knowledge.

Extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) is a transient sequence of acoustic pulses with high peak pressure (100 MPa) followed by negative pressure (5-10 Mpa) with energy density between 0.003-0.89 mJ/mm^2 [33]. Based on the design of the appliance, ESWT can be classified as focused or radial ESWT. These differ in depth of penetration, focusing of energy, and intensity. When it comes to syndrome alleviation and functional recovery in CTS, the radial ESWT was shown to be superior to the focused ESWT [34]. Radial ESWT produces better results for patients with moderate CTS than those with mild CTS [33]. Studies show that ESWT is more effective than sham therapy and wrist splint [35, 36]. No difference was found in comparison with CSI in one meta-analysis [35], however another study showed that ESWT was better than CSI in improving pain and distal motor latency [37]. Regarding the management of nerve injuries, ESWT promotes axonal regeneration of peripheral nerves through a cascade of molecular reactions improving conduction velocity and amplitude [38, 39]. ESWT safety remains controversial because of a few animal studies in which damage to myelin sheaths was found after high intensity therapy[36]. ESWT seems to be promising but further research is needed, especially considering safety issues.

Hydrodissection

Hydrodissection is a minimally invasive alternative to steroid injection [40]. It is a procedure of injecting hyaluronidases into anatomic spaces to facilitate dissection and adhesiolysis. In the case of CTS, fluid is injected between the median nerve and transverse carpal ligament and underlying tendons. Hyaluronidases can depolarize hyaluronic acid leading to its degradation [41]. The rationale behind this treatment is that hyaluronidase injection may interrupt adhesions and facilitate resorption of excess fluid and blood [42], thus reducing the symptoms. Hyalase + 10 ml saline hydrodissection was shown to be more effective than 10 ml saline hydrodissection alone in improving VAS, functional disability score, and nerve conduction [41]. Another study has shown that 5 ml ultrasound guided saline hydrodissection is more effective than 5 ml ultrasound guided subcutaneous injection [43], proving the relevance of application site.

Kinesiology taping

Kinesiology taping is a non-invasive method of treatment developed to provide an external, dynamic support and protection to a specific area of the body. The application of kinesiology taping varies depending on its aim but overall it consists of applying adhesive, elastic tape with certain degree of stretch over a specific area in certain position of the body part [44]. According to Aktürk *et al*., the application of kinesiology taping in CTS can alleviate symptoms by reducing pressure on the nerve by lengthening the transverse carpal ligament, regulating edema, and improving blood flow and lymphatic circulation [45]. Kinesiotaping with splinting was shown to be more effective than splinting alone in symptom reduction, improving functional status score and resulting in electrophysiological improvement in two RCTs [45, 46], but another RCT did not show benefits of KT and splint use over placebo KT, splint or splinting alone [47]. Further research regarding kinesiotaping should focus on proving this initial hypothesis in connection with MRI or Doppler ultrasound studies.

Corticosteroid injection

Corticosteroid injections (CSI) are a common treatment for CTS. The injection can be guided by ultrasound imaging or by landmarks [48]. RCT found that US-guided injection was superior to landmark injection in improving BCTQ score, functional status [49], symptom severity [48], and nerve conduction velocity [50] while other RCTs produced the opposite results [51, 52]. The goal of the procedure is to deliver corticosteroid near the median nerve inside the carpal tunnel. When it comes to the application above or under the median nerve, the effects of the US-guided injection, proximal and distal injections [53] were the same [54]. Injections are relatively safe, but they provide only short-term relief [55]. The most frequent adverse effects are pain in the hand or a region of injection and possible infection. Alleviation of symptoms is obtained mainly through reducing edema, and improving spatial relation between the median nerve and tendons [56]. The improvements caused by an injection are short-term (> 6 months) [57]. Compared to other interventions, CSI shows better outcome to splint alone at 6 weeks [58] and injection and splint shows better outcome than splint alone [59], however the evidence is not homogenous [60]. Adding an injection during surgery was proven as effective as surgery alone [61]. CSI should be considered as a supportive treatment, especially as a modality to alleviate severe symptoms.

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Platelet-rich plasma injection

The extracted plasma portion contains a high concentration of platelets and growth factors that may play crucial roles in tissue regeneration [62]. Growth factors are effective in managing inflammation and promoting wound healing. PRP improved the clinical condition of the patients and was beneficial for patients with mild-to-moderate CTS [63, 64]. The *in vivo* studies of the effects of PRP injection demonstrated improved Schwann cell proliferation, function, and migration. PRP improved symptom severity scale [62, 65] but not functional status scale. VAS and nerve conduction studies were no different compared to controls [65]. Basic science research have found that PRP has modulatory effects on neuroinflammatory environment. They assist with tissue healing and promote axon regeneration [62, 65]. This can explain why PRP adjuvant to surgery improves hand grip strength to pre-operative levels in 6 weeks compared to surgery alone [66]. It is also hypothesized that growth factors released after PRP injection might alleviate nerve ischemia by protecting the blood-nerve barrier [63]. Compared to other treatment modalities PRP with splinting and 5% dextrose do not provide for a better functional recovery [67, 68], but reduce the cross sectional area of the median nerve [69]. Studies have shown that PRP and splint combination was more effective than splint alone [70]. PRP can be effective as an adjuvant to other therapies, promoting neural tissue regeneration.

Low level laser therapy

Low level laser therapy (LLLT) uses red or near-infrared lasers (wavelength 600-1070 nm). The rationale for the use of LLLT in CTS management is its ability to produce biophysical effects on neural tissue that lead to nerve cell regeneration, peripheral nerve regrowth, and functional improvements [71]. In animal studies, LLLT has shown wound healing stimulatory properties by increasing collagen synthesis with utility in reducing edema formation and inflammation [72]. Studies on rats have shown an increase in myelin production and reduction of retrograde degeneration of motor neurons. Other possible mechanisms include selective inhibition of nociceptive activation at peripheral nerves and improvement in blood circulation [73]. These effects can be potentially advantageous in CTS patients, but the search for this review provided no evidence to support any clinical effect of LLLT in treating CTS [74]; no difference compared to placebo [72, 75] or LLLT combined with splinting to splinting alone [71, 76]. Only one systematic review has shown that LLLT is more effective than placebo in very short term (< 5 weeks), following which the effect tends to subside [77]. LLLT, despite its low cost and low risk of adverse effects should be abandoned as a treatment for CTS.

Splints

Wrist splinting is the most common conservative method used in the treatment of CTS [78]. Splint is an orthotic device applied externally, i.e., to the wrist of a CTS patient. The splint with a metacarpophalangeal unit is more effective than thermoplastic wrist splint in pain reduction and DASH score with no difference in grip strength and pinch strength [78]. It can modify the structural and functional characteristics of the neuromuscular and skeletal systems [79]. The main rationale behind the use of splints in CTS patients is the prevention of extensive flexion and extension of the wrist that causes an increase in the pressure inside the carpal tunnel. Sixty days of using a stretching splint has been known to reduce the need for surgery 2 to 1 compared to stretching and NSAIDs [80]. Splints are also commonly used after surgical retinaculum release where they theoretically provide safety regarding flexor tendon bowstringing to prevent nerve subluxation and thus reduce postoperative pain. However, the lack of orthosis compared to removable orthosis and nonremovable orthosis produced no change in outcome up to 12 months after mini-open carpal tunnel release [81]. On the other hand, splints can increase the time needed to return to work and can cause unnecessary additional indisposition [81]. Because splints may reduce patient's activity and performance of daily tasks, it is important not to rely on them as the only way of treatment and use them as a way to improve such issues as sleep disturbance. Gradual return to full functionality should be advised.

Manual therapy and neurodynamics

This review is limited to the methods based on the current standards recommended by the International Federation of Orthopedic Manipulative Physical Therapists Incorporated (IFOMPT). Manual therapy can improve the local range of motion and mechanosensitivity, reduce spinal cord hyperexcitability, and facilitate modulation of the central nervous system pain processing [82]. In various studies, groups that integrated joint mobilization performed better than the control group in pain reduction, subjective symptoms, and functional status [83, 84] but no difference was found in 2-point discrimination [85]. Cadaveric studies discovered that neurodynamic techniques are effective on fluid dispersion in the median nerve at the level of the carpal tunnel, with no difference between sliding and tensioning [86]. The same results were found at the ankle level regarding the tibial nerve [87]. Nerve mobilizations can also facilitate intraneural fluid dispersion at the level of the nerve root as demonstrated in the studies by Gilbert *et al.* Repetitive straight leg raise (SLR) induced a significant increase in longitudinal fluid dispersion in the L4 nerve root of human cadaveric specimen [88]. These results offer a clinical mechanism for the reduction of intraneural edema,

which is a clinical presentation of CTS. Neurodynamic techniques were found to induce median nerve excursion *in vivo* [89]. However, complex biomechanical effect in peripheral nerves [90], along with biochemical changes may play a crucial role regarding the therapeutic effect. Cyclic stretching of nerves was found to promote axonal growth and increase activating transcriptor factor-3 (ATF3) [91]. Two RCTs found the neurodynamic techniques to be more effective than sham therapy [92] or no therapy [93] in improving nerve conduction, pain assessment, 2-point discrimination, symptom severity, and functional status, but a systematic review found no conclusive findings due to methodological limitations in the current body of research [94]. Manual mobilizations of the carpal bones were found to produce an increase in the carpal tunnel cross-sectional area and anteroposterior diameter *in vivo* [95] as well as in cadaveric studies [96]. Manual therapy and surgery had similar effectiveness when it comes to self-reported improvement of function, symptom severity, and pinch-tip grip force [97]. Although for the purposes of this review we only chose studies following the IFOMPT standards, it is unclear which techniques or their dosage are effective. Manual therapy seems to work well with multifactorial conditions, such as CTS, but the current body of knowledge does not provide any clear evidence for the most effective time or area of its application.

Ultrasound and phonophoresis

The ultrasound device converts electrical energy to the piezoelectric acoustic wave, which is then absorbed by tissues of varying impendency to impact heat generation in different tissues. Phonophoresis combines ultrasound via topical anti-inflammatory drugs. Sound waves enhance cutaneous drug absorption [95]. Ultrasound in CTS may have beneficial effects because it stimulates nerve regeneration, increases nerve conductivity, and reduces inflammatory processes [99]. Analgesic effects may be related to increased tissue metabolism and capillary permeability and also thermal effects thus increasing the pain threshold [100]. Despite these findings, the studies examined show no difference between US and phonophoresis in the treatment of CTS [98] and no difference between continuous, pulsed, or sham US combined with splinting [101, 102]. US and phonophoresis do not provide any advantage in the treatment of CTS and thus their application should be reconsidered.

CONCLUSIONS

CTS is common condition that affects women more often than men, with variable clinical presentation, often including sensory and motor symptoms distal to the lesion site. Based on the current body of knowledge, it has been concluded that the conservative CTS treatment is very safe, but the effectiveness of the methods reviewed in this paper differs. Promising first results motivate the need for further research on novel treatment methods but more conclusive and repeated research results are needed to provide a clinical framework for patient allocation and decisions regarding the treatment choices.

Conflict of interest

Absent.

Financial support

Absent.

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