Carpal Tunnel Syndrome: A Summary of Clinical Practice Guideline Recommendations

Using the Evidence to Guide Physical Therapist Practice

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Carpal tunnel syndrome (CTS) is the most common upper extremity nerve compression syndrome. Patients with CTS experience reduced sensation, dexterity, and function. Irreversible changes in nerve structure and function due to demyelination and axonal damage can occur in long-standing cases. Published in the May 2019 issue of *JOSPT*, clinical practice guidelines for CTS summarize the best available evidence on incidence and prevalence, pathophysiology, classification, risk factors, examination techniques, and interventions. These guidelines provide practical recommendations for physical therapy examination, diagnosis, and treatment.

WHAT WE KNEW

We knew there was significant evidence on physical therapy management of CTS, but it had not been used to create clinical practice guidelines on this subject.

WHAT WE DID

We conducted a systematic review for each of the areas presented in the guidelines, including articles published prior to November 2018. Articles that met the inclusion criteria were scored and assigned a level of evidence. Information was summarized and recommendations were made.

WHAT WE FOUND

The clinical exam should include a select battery of well-characterized diagnostic tests and outcome measures. The best available evidence supports use of a nighttime orthosis that places the wrist at or near a neutral, comfortable position. For some individuals with CTS, nonsurgical management is curative; however, more than 50% of patients undergoing nonsurgical management progress to surgery within 1 year.

Factors associated with failed nonsurgical management include (1) higher initial scores on the Boston Carpal Tunnel Questionnaire (CTQ)-symptom severity scale that do not improve, (2) duration of symptoms greater than or equal to 1 year, (3) a positive Phalen test, (4) greater intensity of nighttime symptoms, (5) thenar atrophy, and (6) more than 1 prior failed nonsurgical intervention.

BOTTOM LINE FOR PRACTICE

Examination for CTS should include a thorough history and symptom assessment, the Katz hand diagram, static 2-point discrimination, monofilament testing, the Phalen test, the Tinel sign, the carpal compression test, and the wrist ratio index, as well as the CTQ-symptom severity scale and CTQ-functional scale or the Disabilities of the Arm, Shoulder and Hand questionnaire. Dexterity may be assessed using the Purdue Pegboard or the Dellon-modified Moberg Pickup Test. Baseline grip and 3-point or tip pinch strength may also be assessed.

Individuals with severe CTS, as evidenced by thenar atrophy or electrodiagnostic findings, should be referred to a physician for surgical consultation. Individuals with CTS should be provided with a wrist orthosis, worn at night with the wrist situated comfortably at or near a neutral position. Clinicians should not use low-level laser therapy, iontophoresis, or magnet therapy.

After consideration of associated costs and contraindications, additional nonsurgical interventions may be added. These include modification of the orthosis design and prescription, ergonomic interventions, superficial heat, interferential current, phonophoresis, manual therapy, and exercise (lumbrical or general stretching). Patients who regress or do not improve should be referred to a hand surgeon. A flow chart summarizing key elements of diagnosis and treatment of CTS is provided on the next page.

This *JOSPT* Perspectives for Practice was written by a team of *JOSPT*'s Special Features Editors Alexander Scott, PhD, BSc(PT), and Kathryn Sibley, PhD, and staff, using material contributed by guidelines[1] author Mia Erickson, PT, EdD. The flow chart on the following page was produced by Kate Minick, PT, DPT, OCS, of Intermountain Healthcare, Rehabilitation Services, Salt Lake City, UT.

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Hand Pain and Sensory Deficits: Carpal Tunnel Syndrome (CTS) Care Process Model

Component 1: Diagnosis/Classification of CTS: Evaluation of Clinical Findings

Diagnosis
- Detailed history, including duration, location, and severity of symptoms and history of prior interventions
- Perform upper-quarter screening and rule out cervical radiculopathy and thoracic outlet, pronator teres, ulnar, and radial tunnel syndromes
- Semmes-Weinstein monofilament testing (SWMT): use 2.83 (sensitivity, 98%) or 3.22 (specificity, 97%) monofilament to assess light touch sensation – A
- Static 2-point discrimination on middle finger (higher specificity versus sensitivity) – A
- Katz hand diagram (sensitivity, 75%; specificity, 72%), Phalen test (sensitivity, 68%; specificity, 73%), Tinel sign (sensitivity, 50%; specificity, 77%), carpal compression test (sensitivity, 64%; specificity, 83%) – B
- Age (>45 y), shaking hands to relieve symptoms, sensory loss in thumb, wrist ratio index (>0.67), scores from Boston Carpal Tunnel Questionnaire-symptom severity scale (CTQ-SSS; >1.9) – B
  - 3 positive: sensitivity, 0.98 and specificity, 0.54; 4 positive: positive likelihood ratio = 4.60; 5 positive: sensitivity, 0.18 and specificity, 0.99
- Baseline grip and 3-point or tip pinch strength – C

Mild
- Intermittent symptoms

Moderate
- Constant symptoms
- When suspecting moderate CTS, use SWMT with a 3.22 filament as normal on any radial finger; diagnostic accuracy, 90% – A

Severe
- Thenar muscle atrophy
- When suspecting severe CTS, use SWMT with a 3.22 filament as normal on any radial finger; diagnostic accuracy, 90% – A

Component 2: Outcome Assessment

Patient-Reported Outcome Measures – B
- CTQ-SSS: assess symptoms and change in individuals managed surgically or nonsurgically
- Boston Carpal Tunnel Questionnaire-functional scale: assess function and change following CTR surgery
- Disabilities of the Arm, Shoulder and Hand questionnaire: assess function and change following CTR surgery

Physical Impairment Measures
- Do NOT use lateral pinch as outcome – A
- Do NOT use grip strength for change less than 3 months following CTS surgery – B
- Do NOT use threshold or vibration testing to assess change – C
- Use Phalen test to assess long-term change following CTS surgery – C

Physical Performance Measures – C
- Purdue Pegboard: dexterity (compare with established norms)
- Dellon-modified Moberg pick-up test: dexterity (compare with established norms; can be used to assess change following CTS surgery)

Component 3: Intervention Strategies

Education
- Effects of mouse use and alternate strategies – C
- Use of keyboards with reduced strike force – C
- Pathology, risk identification, symptom self-management, aggravating postures/activities – C

Orthoses
- Neutral-positioned wrist orthosis worn at night for short-term relief and functional improvement – B
- If night-only use is ineffective, include daytime, symptomatic, or full-time use for mild to moderate CTS – C
- If no relief, add metacarpophalangeal joint immobilization or modify wrist joint position – C
- Recommended for women with CTS during pregnancy with postpartum follow-up – C

Superficial heat: short-term symptom relief – C

Microwave or shortwave diathermy: short-term pain and symptom relief for mild to moderate CTS – C

Interferential current: trial for short-term pain relief – C

Phonophoresis: clinical symptom relief for mild to moderate CTS – C

Manual therapy: short-term relief for mild to moderate CTS – C
- Can include soft tissue mobilization at sites of potential median nerve entrapment and cervical spine stretching and mobilization

Orthotic/stretching program: for short-term symptom relief for mild to moderate CTS in patients without thenar atrophy and with normal 2-point discrimination – C

Not Recommended
- Low-level laser therapy or other nonlaser light therapy – B
- Thermal ultrasound for mild to moderate CTS – C
- Iontophoresis for mild to moderate CTS – B
- Use of magnets – B

Based on the guidelines, the grades in this flow chart may be translated as follows: A, strong evidence; B, moderate evidence; C, weak evidence; D, conflicting evidence; F, expert opinion. Figure produced for *JOSPT* by Kate Minick, PT, DPT, OCS, of Intermountain Healthcare, Rehabilitation Services, Salt Lake City, UT.

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ORIGINAL ARTICLE

Effectiveness of manual therapy versus surgery in pain processing due to carpal tunnel syndrome: A randomized clinical trial

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Abstract

Background: People with carpal tunnel syndrome (CTS) exhibit widespread pressure pain and thermal pain hypersensitivity as a manifestation of central sensitization. The aim of our study was to compare the effectiveness of manual therapy versus surgery for improving pain and nociceptive gain processing in people with CTS.
Methods: The trial was conducted at a local regional Hospital in Madrid, Spain from August 2014 to February 2015. In this randomized parallel-group, blinded, clinical trial, 100 women with CTS were randomly allocated to either manual therapy ($n = 50$), who received three sessions (once/week) of manual therapies including desensitization manoeuvres of the central nervous system, or surgical intervention ($n = 50$) group. Outcomes including pressure pain thresholds (PPT), thermal pain thresholds (HPT or CPT), and pain intensity which were assessed at baseline, and 3, 6, 9 and 12 months after the intervention by an assessor unaware of group assignment. Analysis was by intention to treat with mixed ANCOVAs adjusted for baseline scores.
Results: At 12 months, 95 women completed the follow-up. Patients receiving manual therapy exhibited higher increases in PPT over the carpal tunnel at 3, 6 and 9 months (all, $p < 0.01$) and higher decrease of pain intensity at 3 month follow-up ($p < 0.001$) than those receiving surgery. No significant differences were observed between groups for the remaining outcomes.
Conclusions: Manual therapy and surgery have similar effects on decreasing widespread pressure pain sensitivity and pain intensity in women with CTS. Neither manual therapy nor surgery resulted in changes in thermal pain sensitivity.
Significance: The current study found that manual therapy and surgery exhibited similar effects on decreasing widespread pressure pain sensitivity and pain intensity in women with carpal tunnel syndrome at medium- and long-term follow-ups investigating changes in nociceptive gain processing after treatment in carpal tunnel syndrome.

1. Introduction

Carpal tunnel syndrome (CTS) is a condition resulting in a variety of symptoms including numbness/tingling, pain and motor control loss leading to decreased function and disability. The prevalence of CTS ranges from 6% to 12% in the general population (Thiese et al., 2014). The financial costs associated with lost work days secondary to CTS ranges from $45,000 to $89,000 over a 6-year period (Foley et al., 2007). The overall cost associated with CTS in the United States exceeds $2 billion annually (Stapelton, 2006).

The etiology of CTS has historically been linked to median nerve compression at the carpal tunnel; however, recent evidence suggests that CTS is a complex pain syndrome involving sensitization processes (de-la-Llave-Rincón et al., 2012), since women with CTS exhibit widespread pressure pain hypersensitivity (Fernández-de-las-Peñas et al., 2009), thermal pain hyperalgesia (de-la-Llave-Rincón et al., 2009) and enhanced wind-up in extra-median nerve territories (Zanette et al., 2010). Furthermore, it has recently been observed that subgroups of women with CTS exhibiting higher widespread pressure hypersensitivity and thermal hyperalgesia exist (Fernández-de-las-Peñas et al., 2016).

Management strategies for CTS include conservative or surgical interventions (Huisstede et al., 2014). While surgery continues to be the most common intervention, there is much debate surrounding its efficacy, as 33% of individuals receiving surgery had not returned to work at 2 months (Parot-Schinkel et al., 2011). Furthermore, both strategies are beneficial for CTS, but surgery seems to be slightly superior to conservative treatment at long-term (Shi and MacDemid, 2011). Nevertheless, it should be considered that the vast majority of subjects with CTS attempt to avoid surgery (Jarvik et al., 2009). Physical therapy is often used for the treatment of CTS; however, there is limited evidence supporting the use of exercise and mobilization techniques (Page et al., 2012a). Similarly, although splinting and injections seem to also be beneficial at short-term, their effects are no longer present at long-term (Page et al., 2012b).

Previous studies comparing conservative versus surgery for CTS have applied localized treatments, i.e. ultrasound, splinting, laser or exercises, mainly focused to the wrist/hand. According to recent theories supporting that CTS is associated with central sensitization, it is conceivable that therapeutic strategies should consider a comprehensive nociceptive pain rationale by including interventions targeted at desensitizing central nervous system (Nijs and Van Houdenhove, 2009). A recent randomized clinical trial compared the application of manual therapies including desensitization manoeuvres of the central nervous system versus surgery in a sample of women with CTS and found that manual therapy obtained better short-term, but similar long-term, effects on pain and function as compared to surgery (Fernández-de-las-Peñas et al., 2015).

There is some evidence suggesting that manual therapies integrating physiology of pain and sensitization procedures are able to attenuate pressure and thermal sensitivity (Coronado et al., 2012; Bialosky et al., 2014). A previous study found a decrease in heightened pain sensitivity associated with clinical improvements in subjects with clinical symptoms of CTS after the application of manual therapy (Bialosky et al., 2011). However, this was a non-controlled trial and only included immediate post-treatment outcomes. There is no evidence examining if subjects with CTS receiving manual therapy or surgery will exhibit changes in pressure and thermal sensitivity associated with changes in pain. Therefore, the purpose of our randomized clinical trial was to compare the effects of manual therapy versus surgery for improving pain and nociceptive gain processing in CTS. A secondary objective was to determine if changes in pain were associated with changes in pressure or thermal pain hyperalgesia.

2. Methods

2.1 Participants

A randomized parallel-group trial was conducted (clinical registry NCT02219919). Consecutive women recruited from a local regional Hospital (Madrid, Spain) with clinical and electrophysiological findings of CTS were screened for eligibility criteria. To be eligible, individuals had to exhibit pain and paresthesia in the median nerve distribution for at least 6 months, positive Tinel sign, and positive Phalen sign. Additionally, the electro-diagnostic examination had to reveal deficit of sensory and motor median nerve conduction (i.e. median nerve sensory conduction velocity <40 m/s and median nerve distal motor latency >4.20 ms) according to guidelines of the American Association of Electrodiagnosis, American Academy of Neurology, and the American Physical Medicine and Rehabilitation Academy (Jablecki et al., 2002). Patients were classified as minimal

(abnormal segmental-comparative tests only), moderate (abnormal median nerve sensory velocity conduction and distal motor latency) or severe (absence of median nerve sensory response and abnormal distal motor latency) CTS (Padua et al., 1999).

Participants were excluded if they exhibited any of the following criteria: (1) any sensory and/or motor deficit in either ulnar or radial nerve; (2) age >65 years; (3) previous surgery or steroid injections in the wrist; (4) multiple diagnoses on the upper extremity (e.g. co-existing cervical radiculopathy); (5) cervical, shoulder, hand trauma; (6) systemic disease causing CTS (e.g. diabetes mellitus, thyroid disease); (7) comorbid musculoskeletal medical conditions, e.g. rheumatoid arthritis, or fibromyalgia; (8) pregnancy; or (9) male gender. All subjects signed an informed consent prior to inclusion in the trial. The local human research committee (HUFA 12/14) approved the study project.

2.2 Randomization and allocation

Patients were randomly assigned to receive manual therapy or surgery. Concealed allocation was conducted using a computer-generated randomized table of numbers created prior to the start of the data collection by an external researcher not involved in recruitment. Individual and sequentially numbered index cards with random assignment were prepared, folded and placed in sealed opaque envelopes. A second researcher opened the envelope and proceeded with treatment according to group assignment. We blinded clinicians who obtained follow-up information to group allocation.

2.3 Interventions

Patients allocated to the manual therapy group received three treatment sessions of manual therapies including desensitization manoeuvres of the central nervous system of 30-min duration, once/week. All treatments were applied by physical manual therapists with more than 10 years of experience in manual therapy approaches. The desensitization manoeuvres consisted of soft tissue mobilization and nerve/tendon gliding exercises including manual techniques directed at anatomical sites of potential entrapment of the median nerve such as scalene muscles, pectoralis minor muscle, biceps brachii muscle, bicipital aponeurosis, pronator teres, wrist flexor musculature, transverse carpal ligament, palmar aponeurosis or lumbricals muscles (Moraska et al., 2008). All these interfaces were treated according to the following clinical findings: pain on palpation and reproduction of sensory or motor symptoms of patients. Finally, tendon/nerve gliding interventions of the upper extremity were also applied. The nerve/tendon gliding exercises targeted the median nerve (Coppieters and Alshami, 2007) and were performed as follows: shoulder girdle depression, gleno-humeral abduction and lateral rotation, supination of the forearm, wrist, thumb and fingers extension (Coppieters et al., 2009). From that position, concurrent elbow flexion and wrist extension was alternated with concurrent elbow extension and wrist flexion (Coppieters and Butler, 2008). Speed and amplitude of movement were adjusted to avoid pain during the intervention. The intervention was completed over a period of 5–10 min in two sets of 5 min each with 1 min rest between sets. Finally, the third and last treatment appointments included an educational session on performing the tendon/nerve gliding exercise as homework twice per day during the first month after discharge. Participants were asked to not modify any work or activity levels during all the follow-up period.

Patients randomly allocated to the surgery group received endoscopic decompression and release of the carpal tunnel following international guidelines. For pragmatic reasons and because no evidence supports any particular surgical procedure (Zuo et al., 2015), surgery was based on each surgeon's and patient's preference. All surgeons were experienced with at least 10 years of practice focusing on hand surgery. Patients allocated to this group also received the same educational sessions for performing the tendon/nerve gliding exercises as the manual therapy group in the same dosage.

2.4 Outcomes

Outcomes were assessed at baseline, and 3, 6, 9 and 12 months after the end of the treatment. Our primary outcome was pressure pain sensitivity assessed with pressure pain thresholds (PPTs). PPTs were assessed bilaterally over the median, radial and ulnar nerves, C5-C6 joint, carpal tunnel and tibialis anterior muscle following previous reported guidelines (Fernández-de-las-Peñas et al., 2009, 2016) with an electronic algometer (Somedic AB©, Farsta, Sweden). The pressure was increased approximately at a rate of 30 kPa/s. Participants were instructed to press the switch when the sensation first changed from pressure to pain. The mean of three trials was calculated on each point. Since no side-to-side differences are found in PPTs, we pooled data of both sides for the

analysis. A 30-s resting period was allowed between each measure. The reliability of pressure algometry has been found to be high (ICC: 0.91, 95%CI 0.90–0.96) (Jones et al., 2007).

Secondary outcomes included the intensity of pain and thermal pain sensitivity. An 11-points Numerical Pain Rating Scale (NPRS, 0: no pain; 10: maximum pain) was used to assess the patients' current level of pain and the worst and lowest level of pain experienced in the preceding week. The mean value of the three scores was used in the analysis at each follow-up period (Jensen et al., 1999). For patients with bilateral symptoms, we assigned the study hand on the basis of the more self-rated symptomatic hand; if symptoms were equivalent, the mean pain of both hands was used. Since no minimal clinically important difference (MCID) has been determined for hand pain, a change of two points or a 30% decrease in the intensity of pain from baseline was considered as a meaningful clinical change (Farrar et al., 2001).

Thermal pain thresholds were tested bilaterally over the carpal tunnel and the thenar eminence as in previous studies (de-la-Llave-Rincón et al., 2009; Fernández-de-las-Peñas et al., 2016) with a Thermotest System (Somedic AB©). Participants were instructed to press a hand-controlled switch when the sensation changes from heat/cold to heat/cold pain (heat or cold pain threshold, HPT/CPT). The mean of three trials was calculated on each point. Since no side-to-side differences are found in HPT or CPT, we pooled data of both sides for the analysis. A rest of 5 s occurred between trials. Park et al. (2001) reported a good reliability of thermal pain thresholds on the volar aspect of the forearm in healthy subjects.

2.5 Treatment side effects

Patients were asked to report any adverse event that they experienced either after the intervention or during any other part of the study. In the current study, an adverse event was defined as sequelae of medium-term in duration with any symptom perceived as distressing and unacceptable to the patient and required further treatment.

2.6 Sample size determination

The sample size was calculated using Ene 3.0 software (Autonomic University of Barcelona, Spain). The calculations were based on detecting differences of 100 kPa at post-data on the main outcome, assuming a standard deviation of 136 kPa, a 2-tailed test, an alpha level (α) of 0.05, and a desired power (β) of 90%. The estimated desired sample size was calculated to be at least 40 participants per group. A dropout rate of 20% was expected, so 50 patients were included in each group at baseline. We chose this level of change since Walton et al. (2011) reported a minimal detectable change (MDC) for PPT over the tibialis anterior muscle of 97.9 kPa.

2.7 Statistical analysis

Statistical analysis was performed using SPSS software, version 20.0 (Chicago, IL, USA) and it was conducted according to intention-to-treat analysis for patients in the group to which they were allocated. When any data was missing, multiple imputation method was used. Mean, standard deviations and/or 95% confidence intervals were calculated for each variable. The Kolmogorov–Smirnov test showed a normal distribution of the quantitative data ($p > 0.05$). Baseline demographic and clinical variables were compared between both groups using independent Student *t*-tests for continuous data and χ^2 tests of independence for categorical data. Our primary evaluation was repeated measured analyses of covariance (ANCOVA) with time (baseline, 3, 6, 9, 12 months) as the within-subjects factor and group (manual therapy, surgery) as the between-subject factor and adjusted for baseline outcomes for evaluating between-group differences in all the outcomes. To enable comparison of effect sizes, standardized mean score differences (SMDs) were calculated by dividing the mean between-group score differences by the pooled standard deviation from the change score. In general, a p value <0.05 was considered as statistically significant for the main hypothesis of interest (Group × Time interaction); however, for *post hoc* analysis a Bonferroni-corrected α level of 0.01 (5 repeated measured moments) was used.

Finally, to determine the relationship between changes in pain intensity and changes in the remaining variables, several Pearson product-moment correlation coefficients were calculated. A linear regression analysis was conducted between those variables showing a significant association with changes in the outcomes during the trial.

3. Results

Between August 2014 and February 2015, 130 consecutive patients with CTS were screened for eligibility criteria. One hundred (77%) satisfied all inclusion criteria, agreed to participate and were

randomly allocated into manual therapy ($n = 50$) or surgery ($n = 50$) group. Randomization resulted in similar baseline characteristics for all variables (Table 1). In the group receiving manual therapy, two patients were lost at 6 months follow-up and 1 at 12 months because they received local injection of steroids and surgery, respectively. Similarly, two patients allocated to the surgical group were lost at 1-year follow-up because they received a second intervention in the hand. None of the participants in either group reported other intervention during the study, excluding the use of NSAIDs sporadically. No clinically important adverse events and no surgical complications were reported during the trial including the 12 months follow-up. The reasons for ineligibility can be found in Fig. 1, which provides a flow diagram of patient recruitment and retention.

Adjusting for baseline outcomes, the mixed model ANCOVA observed a significant Group*Time interaction for PPT over the carpal tunnel ($F = 11.642$; $p < 0.001$); but not for PPT over the median nerve ($F = 0.901$; $p = 0.345$), ulnar nerve ($F = 0.120$; $p = 0.730$), radial nerve ($F = 0.186$; $p = 0.667$), C5/C6 joint ($F = 0.750$; $p = 0.389$) or tibialis anterior muscle ($F = 0.129$; $p = 0.720$): patients receiving manual therapy exhibited higher increases in PPT over the carpal tunnel at 3, 6 and 9 months (Δ 185.5 [95%CI 143.7–227.3], $p < 0.001$; 108.5 [95%CI 75.9–141.4], $p < 0.001$; 75.8 [95%CI 57.9–93.7], $p < 0.01$, respectively) than those who received surgery (Fig. 2). The between-group effect sizes were large ($1.1 < SMD < 1.7$) in favour of manual therapy group. Changes in PPT over the medial, radial and ulnar nerve, C5-C6 zygapophyseal joint and tibialis anterior muscle were similar in both groups at all follow-up periods (Table 2).

Table 1 Baseline characteristics by treatment assignment.

	Manual therapy group ($n = 50$)	Surgery group ($n = 50$)
Age (years)	47 ± 10	48 ± 9
Years with pain	3.2 ± 1.7	3.3 ± 1.9
Occupation		
Work at home *n* (%)	25 (50%)	24 (48%)
Secretary/Office *n* (%)	25 (50%)	26 (52%)
Unilateral/bilateral arm distribution *n* (%)		
Unilateral symptoms – right side	10 (20%)	9 (18%)
Unilateral symptoms – left side	7 (14%)	8 (16%)
Bilateral symptoms	33 (66%)	33 (66%)
Severity *n* (%)		
Minimal CTS	18 (36%)	15 (30%)
Moderate CTS	16 (32%)	17 (34%)
Severe CTS	16 (32%)	18 (36%)
Intensity of Hand Pain (0–10)	4.2 ± 1.0	4.4 ± 1.6
Pressure Pain Thresholds (kPa)		
Median Nerve	184.6 ± 59.7	191.0 ± 48.7
Ulnar Nerve	289.2 ± 96.6	295.1 ± 68.5
Radial Nerve	217.2 ± 73.6	230.4 ± 61.0
C5-C6 zygapophyseal joint	169.7 ± 46.7	173.3 ± 47.6
Carpal Tunnel	335.5 ± 88.5	340.8 ± 108.9
Tibialis anterior muscle	319.7 ± 91.3	333.9 ± 77.0
Heat (HPT) and Cold (CPT) Pain Thresholds (°C)		
HPT carpal tunnel	40.3 ± 3.1	39.7 ± 2.9
CPT carpal tunnel	19.7 ± 5.6	18.6 ± 7.9
HPT thenar eminence	40.1 ± 8.5	40.4 ± 3.0
CPT thenar eminence	19.0 ± 6.7	19.8 ± 7.5

The intention-to-treat analysis also revealed a significant Group × Time interaction for the intensity of pain ($F = 5.735$; $p = 0.019$): women receiving manual therapy exhibited higher decrease at 3 months in pain intensity (Δ −1.5 [95%CI −0.8 to −2.3]; $p < 0.001$) than those receiving surgery (Fig. 3). The between-group effect size was large (SMD: 1.25) in favour of manual therapy group. No significant between-group differences were observed at 6, 9 and 12 months ($p > 0.15$, Fig. 3). Both groups exhibited large within-group effect sizes ($1.30 > SMD > 1.45$) at all follow-up periods.

Finally, no significant changes were observed for neither HPT (carpal tunnel: $F = 0.640$, $p = 0.426$; thenar eminence: $F = 0.667$, $p = 0.616$) or CPT (carpal tunnel: $F = 0.175$, $p = 0.676$; thenar eminence: $F = 0.449$, $p = 0.773$, Table 3, Fig. 4) after the application of manual therapy or surgery.

No association was observed between changes in pain intensity, changes in pressure or thermal pain sensitivity in either group ($p > 0.45$).

4. Discussion

The current randomized clinical trial found that a manual therapy program including desensitization manoeuvres of the central nervous system resulted in similar improvements as surgery on pain intensity and widespread pressure pain sensitivity at mid and long-term follow-up periods. Patients assigned to the manual therapy group exhibited significantly higher decrease of pain intensity at 3 months and significant improvements in PPTs over the carpal tunnel at 3, 6 and 9 months. Neither manual therapy nor surgery resulted in significant changes in thermal pain sensitivity.

It is hypothesized that neurophysiological mechanisms of manual therapy related to its ability for modulating central nervous system pain processing include reduction in pressure sensitivity (increases in PPTs), i.e. a mechanical hypoalgesic effect, and also a

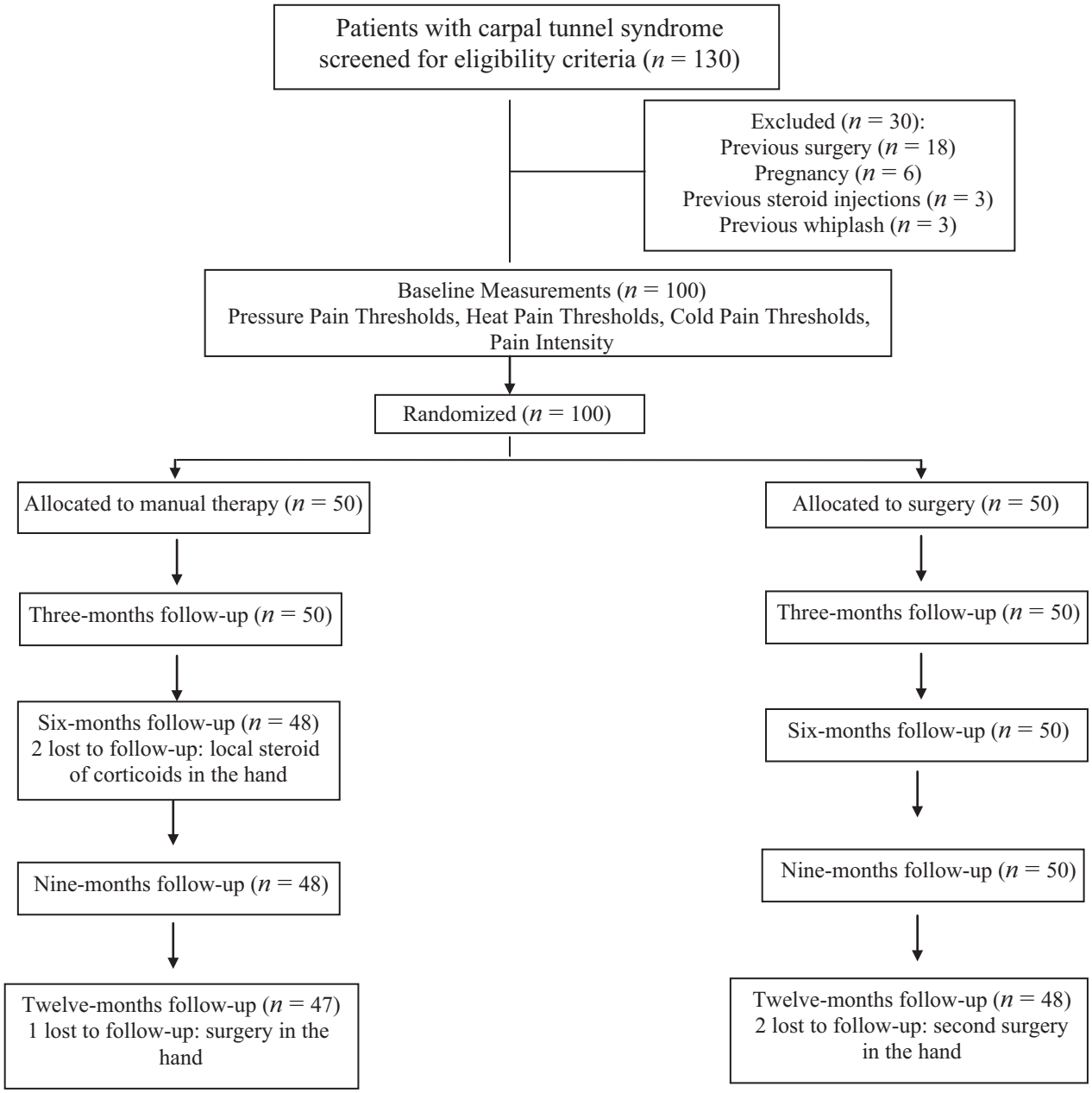

Figure 1 Flow diagram of patients throughout the course of the study.

modulation of thermal pain thresholds (Bialosky et al., 2009). A recent meta-analysis has concluded that spinal manipulative therapy increases PPTs at remote anatomical sites, but not at the local anatomical site (Coronado et al., 2012). However, changes observed in this meta-analysis were small and not clinically relevant. Another recent systematic review found no significant changes on thermal pain thresholds after the application of manual therapy (Voogt et al., 2015). In our trial, we found that both manual therapy and surgery induced similar changes in widespread pressure pain sensitivity in our sample of women with CTS. Nevertheless, it should be recognized that changes in PPTs in both groups did not surpass the MDC proposed by Walton et al. (2011) either for the cervical spine (47.2 kPa) or for the tibialis anterior (97.9 kPa). Our results agree with a previous study showing that changes in PPTs were relatively small immediately after the application of a single neurodynamic intervention in individuals

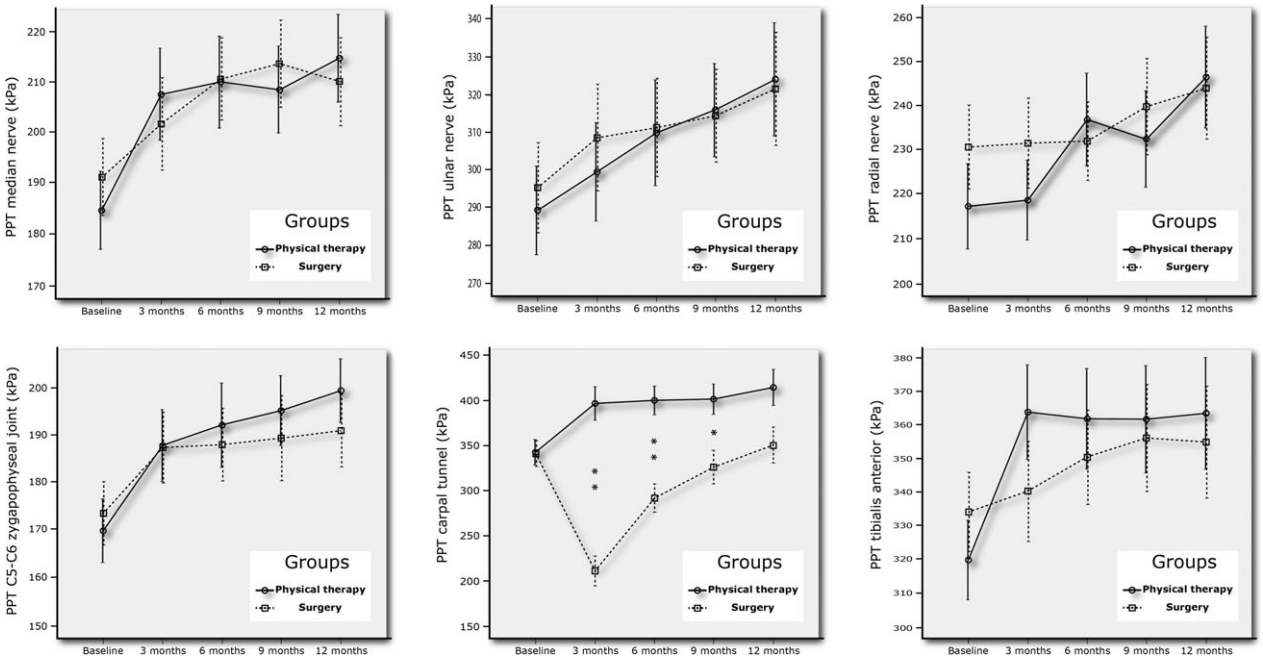

Figure 2 Evolution of widespread pressure pain sensitivity throughout the course of the study stratified by randomized treatment assignment. Data are means (standard error). $^{**}p < 0.001$; $^{*}p < 0.01$.

with sign and symptoms of CTS (Bialosky et al., 2011). Similarly, no relevant changes in PPTs were observed after the application of a nerve tensioner intervention targeting the sciatic nerve in people with spinally referred leg pain (Ridehalgh et al., 2016). However, it is interesting to note that we observed significant changes in PPTs over the carpal tunnel in favour of the manual therapy group at 3, 6 and 9 month follow-up periods. In fact, between-group score differences surpassed the MDC at all follow-ups suggesting a clinical localized hypoalgesic effect over the carpal tunnel with the multimodal manual therapy program used in the current trial. This could be related to a peripheral effect of manual therapy or to the time frame needed for recovering the tissue damage provoked by surgery at the carpal tunnel. It would be expected higher pain sensitivity to pressure over the anatomical area, i.e., the carpal tunnel, receiving the surgical procedure with the consequent post-surgery time recovery. Furthermore, we did not find any change in heat and cold pain thresholds in either group supporting no changes in thermal sensitivity after manual therapy or surgery. Since thermal sensitivity, particularly, cold hyperalgesia is considered a feature of neuropathic pain as a result of peripheral nerve injury (De Medinaceli et al., 1997); it is possible that either treatment was able to reverse the intrinsic damage of the nerve at the carpal tunnel. Since our trial is the first investigating changes in pressure and thermal sensitivity in CTS, no comparison with previous studies using similar surgical interventions can be made.

We observed that both groups experienced significant and clinically important decreases from baseline to follow-up periods on pain intensity, particularly at 6, 9 and 12 months. The magnitude of between-group differences was not significant at mid- and long-terms. It should be noted that the manual therapy group exhibited a greater decrease of pain at 3 month follow-up compared to the surgery group; although the clinical significance of the between-group difference is not clear given the inclusion of the MCID within the 95%CI. The current findings are in agreement with those from a previous clinical trial observing a similar manual therapy program was also more effective at short, but equally effective and mid and long-term, as surgery for improving pain and self-reported function in a different sample of women with CTS (Fernández-de-las-Peñas et al., 2015).

Finally, we did not observe any association between changes in clinical pain intensity and changes in pressure or thermal pain hyperalgesia. Current results agree with a previous study conducted on shoulder pain where no association

Table 2 Pressure pain thresholds (PPT, kPa) at baseline, 3, 6, 9 and 12 months by randomized treatment assignment.

Outcome group	Baseline	3 months	6 months	9 months	12 months
PPT median nerve (kPa)					
Manual therapy	184.6 ± 59.7 (169.3, 199.8)	207.4 ± 72.7 (189.4, 225.5)	209.8 ± 59.5 (193.7, 225.9)	208.3 ± 72.9 (191.3, 224.3)	214.7 ± 69.3 (197.3, 232.0)
Surgery	191.0 ± 48.7 (175.7, 206.3)	201.5 ± 54.6 (183.4, 219.5)	210.6 ± 55.1 (194.5, 226.7)	213.6 ± 44.9 (196.6, 230.6)	210.1 ± 53.2 (192.8, 227.5)
PPT ulnar nerve (kPa)					
Manual therapy	289.2 ± 96.6 (265.7, 312.7)	299.3 ± 110.5 (273.6, 324.9)	309.8 ± 118.6 (282.0, 337.5)	315.6 ± 97.9 (291.3, 339.9)	324.1 ± 121.9 (294.4, 353.7)
Surgery	295.1 ± 68.5 (271.6, 318.6)	308.4 ± 72.4 (280.6, 336.2)	311.2 ± 67.4 (285.5, 336.9)	314.4 ± 73.5 (290.1, 338.7)	321.6 ± 86.7 (291.9, 351.3)
PPT radial nerve (kPa)					
Manual therapy	217.2 ± 73.6 (198.2, 236.1)	218.6 ± 68.4 (200.7, 236.4)	236.7 ± 87.3 (216.3, 257.3)	232.2 ± 94.6 (210.3, 254.1)	246.4 ± 95.6 (223.3, 269.6)
Surgery	230.4 ± 61.0 (211.4, 249.3)	231.3 ± 55.5 (210.8, 251.8)	231.7 ± 58.2 (213.9, 249.5)	239.6 ± 57.0 (217.7, 261.5)	243.9 ± 66.7 (220.7, 267.0)
PPT C5-C6 zygapophyseal joint (kPa)					
Manual therapy	169.7 ± 46.7 (156.5, 182.9)	187.7 ± 57.6 (172.5, 202.8)	192.2 ± 61.1 (174.4, 209.9)	195.1 ± 55.5 (180.4, 209.9)	199.3 ± 56.7 (184.2, 214.3)
Surgery	173.3 ± 47.6 (159.9, 186.7)	187.2 ± 49.4 (172.3, 202.1)	187.8 ± 50.0 (172.5, 203.1)	189.2 ± 65.6 (171.2, 207.2)	190.9 ± 50.3 (175.7, 206.1)
PPT carpal tunnel (kPa)					
Manual therapy	335.5 ± 88.5 (307.6, 363.3)	396.4 ± 153.1 (359.7, 433.0)	400.2 ± 134.9 (368.8, 431.6)	401.7 ± 140.4 (368.6, 434.9)	414.6 ± 166.2 (375.5, 453.7)
Surgery	340.8 ± 108.9 (312.7, 368.9)	210.9 ± 89.5 (177.5, 244.4)	291.7 ± 81.6 (260.1, 323.4)	325.9 ± 104.7 (288.9, 362.9)	350.4 ± 19.9 (310.9, 389.9)
PPT tibialis anterior muscle (kPa)					
Manual therapy	319.7 ± 91.3 (296.0, 343.4)	363.7 ± 120.1 (335.6, 391.7)	361.7 ± 127.5 (331.8, 391.6)	361.6 ± 127.5 (329.8, 393.4)	363.4 ± 127.6 (330.1, 396.6)
Surgery	333.9 ± 77.0 (310.2, 357.6)	340.2 ± 79.7 (310.3, 370.0)	350.3 ± 74.3 (322.2, 378.3)	356.0 ± 92.3 (324.2, 387.8)	354.8 ± 114.6 (321.6, 388.0)

Values are expressed as mean ± standard deviation (95% confidence interval).

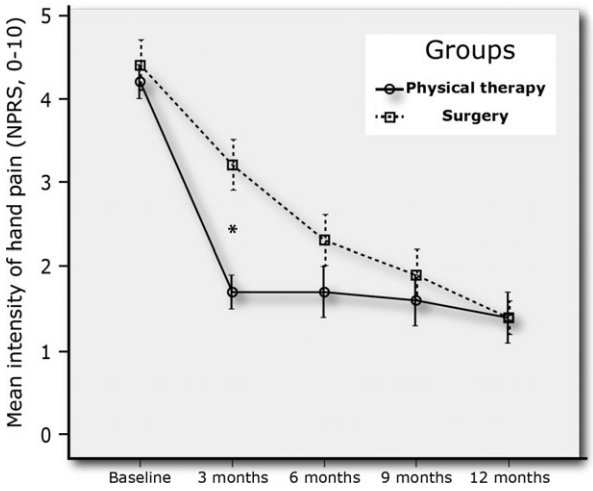

Figure 3 Evolution of pain intensity throughout the course of the study stratified by randomized treatment assignment. Data are means (standard error). *$p < 0.01$.

between pain sensitivity changes and clinical outcomes were identified (Coronado et al., 2015). This may be related to the fact that clinical outcomes such as pain and function do not exhibit an association with neuro-physiological outcomes such as PPTs (Hübscher et al., 2013). It seems that neurophysiological mechanisms related to changes in clinical outcomes are not related to changes in neurophysiological outcomes.

The current trial has potential implications for clinical practice. The use of conservative or surgical procedure for the management of CTS is controversial. It is currently accepted that surgery can result in slightly superior outcomes compared to conservative treatment at long-term (Shi and MacDemid, 2011); however, it should be noted that previous studies comparing conservative interventions versus surgery have primarily used localized wrist interventions such as splints, laser, ultrasound or injections without the application of a comprehensive nociceptive pain rationale. Therefore, the inclusion of data from recent randomized clinical trials, such as the current one, may have an impact on future reviews or meta-analyses.

The results of this trial should be taken considering its strengths and limitations. One of the strengths was that we compared a multimodal and pragmatic manual therapy approach to a common used surgical intervention for CTS allowing generalizability to current clinical practice. Furthermore, different physical therapists and surgeons participated in the management of women in this clinical trial, hence enhancing the generalizability of the current results. Finally, our clinical trial had a high retention rate at 12 month follow-up. Nevertheless, potential limitations should also be considered. First, we only included women recruited from a single local hospital. Although CTS is most predominantly in women, we do not know if men would achieve similar outcomes. In addition, women included in our study may be considered as idiopathic CTS since medical conditions causing CTS were a reason for exclusion. Nevertheless, some causes of median nerve compression, e.g. anatomical variations, were not explored. Second, we do not know the optimal dosage for manual therapy. In the current study, we only applied three sessions of manual therapy according to a protocol used in a previous study (Fernández-de-las-Peñas et al., 2015). It is possible that with more sessions, patients could experience greater improvements in the outcomes since a cumulative effect of manual therapy sessions could be expected.

Table 3 Heat (HPT) and Cold (CPT) Pain thresholds (°C) at baseline, 3, 6, 9 and 12 months by randomized treatment assignment.

Outcome group	Baseline	3 months	6 months	9 months	12 months
HPT carpal tunnel (°C)					
Physical therapy	40.3 ± 3.1 (39.5, 41.2)	40.9 ± 2.7 (40.1, 41.6)	40.6 ± 6.7 (39.0, 42.1)	41.1 ± 2.9 (40.2, 41.9)	41.4 ± 3.2 (40.0, 42.8)
Surgery	39.7 ± 2.9 (38.7, 40.6)	39.9 ± 2.8 (39.1, 40.8)	40.1 ± 2.8 (39.2, 40.9)	40.8 ± 6.3 (39.3, 42.2)	41.4 ± 3.2 (39.7, 42.9)
CPT carpal tunnel (°C)					
Physical therapy	19.7 ± 5.6 (17.9, 21.5)	19.4 ± 7.0 (17.4, 21.5)	19.1 ± 5.8 (17.4, 20.8)	18.6 ± 5.8 (17.4, 20.8)	18.5 ± 6.7 (16.5, 20.4)
Surgery	18.6 ± 7.9 (16.3, 20.9)	20.1 ± 7.1 (18.2, 22.1)	20.2 ± 6.1 (18.4, 21.9)	18.9 ± 6.3 (16.8, 20.9)	18.7 ± 6.9 (16.6, 20.7)
HPT thenar eminence (°C)					
Physical therapy	40.1 ± 8.5 (38.2, 41.9)	40.6 ± 5.9 (39.2, 41.9)	40.7 ± 6.0 (39.4, 42.0)	40.8 ± 3.0 (39.9, 41.7)	41.1 ± 6.3 (39.7, 42.5)
Surgery	40.4 ± 3.0 (39.5, 41.3)	40.8 ± 3.1 (39.4, 42.3)	40.7 ± 2.7 (39.3, 42.1)	41.7 ± 2.9 (39.8, 43.7)	42.2 ± 2.8 (40.7, 43.7)
CPT thenar eminence (°C)					
Physical therapy	19.0 ± 6.7 (17.0, 21.0)	19.1 ± 5.9 (17.3, 20.9)	18.6 ± 6.1 (16.8, 20.3)	18.1 ± 6.9 (16.1, 20.1)	17.9 ± 7.5 (15.9, 19.9)
Surgery	19.8 ± 7.5 (17.7, 21.9)	18.3 ± 7.1 (16.3, 20.3)	18.8 ± 6.4 (16.9, 20.7)	18.0 ± 6.4 (15.9, 20.1)	17.9 ± 6.9 (15.8, 19.9)

Values are expressed as mean ± standard deviation (95% confidence interval).
*Significant between-group differences (ANCOVA, $p < 0.01$).

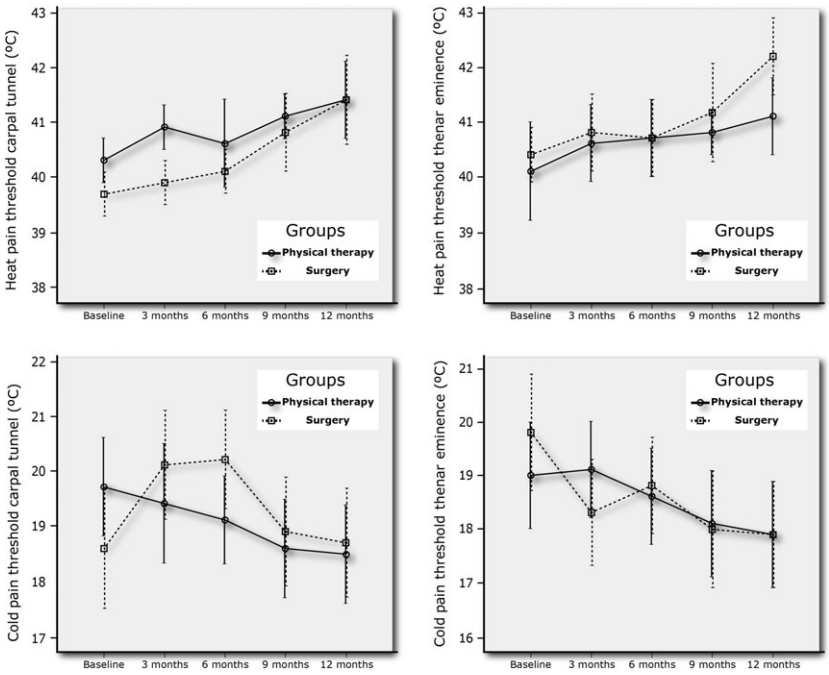

Figure 4 Evolution of thermal pain thresholds (carpal tunnel on left; thenar eminence on right) throughout the course of the study stratified by randomized treatment assignment. Data are means (standard error).

There is no particular dosage for the management of CTS with manual therapy; therefore, future studies should investigate the effects on nociceptive pain processing of different number of treatment sessions. Additionally, the results cannot be attributed only to the manual therapy regimen since patients conducted homework including tendon/nerve gliding exercises, so we should not exclude the contribution of exercises to the current findings. Third, we did not collect psychological outcomes, e.g. depression, anxiety or sleep disorders which could potentially impact those changes in central pain processing. Similarly, we did not collect post-treatment data of the electro-neurological examination. We do not currently know if the manual therapy program applied in the current study would be able to produce changes in this outcome.

5. Conclusions

The results of the current trial suggest that multimodal manual therapy and surgery exhibited similar outcomes in pain and pressure sensitivity at mid- and long-term follow-up periods, but manual therapy exhibited significant better improvements at short-term in pain and localized pressure pain sensitivity, in women with CTS. No changes in thermal pain sensitivity were observed after either manual therapy or surgery.

Author contributions

All authors contributed to the study concept and design. C.F.d.l.P. and J.C. did the statistical analysis. C.F.d.l.P., M.P.C. and F.A.S. contributed to analysis and interpretation of data. C.F.d.l.P. and J.C. contributed to draft the report. C.F.d.l.P., J.A.P. and S.F.N. obtained funding. J.A.P., S.F.N. and C.A.B. provided administrative, technical, and material support. J.A.P. and C.A.B. supervised the study. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

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Manual Therapy Versus Surgery for Carpal Tunnel Syndrome: 4-Year Follow-Up From a Randomized Controlled Trial

César Fernández-de-las-Peñas, José L. Arias-Buría, Joshua A. Cleland, Juan A. Pareja, Gustavo Plaza-Manzano, Ricardo Ortega-Santiago

Objective. No study to our knowledge has investigated the effects longer than 1 year of manual therapy in carpal tunnel syndrome (CTS). The purpose of this study was to investigate the effects of manual therapy versus surgery at 4-year follow-up and to compare the post-study surgery rate in CTS.

Methods. This randomized controlled trial was conducted in a tertiary public hospital and included 120 women with CTS who were randomly allocated to manual therapy or surgery. The participants received 3 sessions of physical therapy, including desensitization maneuvers of the central nervous system or carpal tunnel release combined with a tendon/nerve gliding exercise program at home. Primary outcome was pain intensity (mean and the worst pain). Secondary outcomes included functional status, symptom severity, and self-perceived improvement measured using a global rating of change scale. Outcomes for this analysis were assessed at baseline, 1 year, and 4 years. The rate of surgical intervention received by each group was assessed throughout the study.

Results. At 4 years, 97 (81%) women completed the study. Between-group changes for all outcomes were not significantly different at 1 year (mean pain: mean difference [MD] = −0.3, 95% CI = −0.9 to 0.3; worst pain: MD = −1.2, 95% CI = −3.6 to 1.2; function: MD = −0.1, 95% CI = −0.4 to 0.2; symptom severity: MD = −0.1, 95% CI = −0.3 to 0.1) and 4 years (mean pain: MD = 0.1, 95% CI = −0.2 to 0.4; worst pain: MD = 0.2, 95% CI = −0.8 to 1.2; function: MD = 0.1, 95% CI = −0.1 to 0.3; symptom severity: MD = 0.2, 95% CI = −0.2 to 0.6). Self-perceived improvement was also similar in both groups. No between-group differences (15% physical therapy vs 13% surgery) in surgery rate were observed during the 4 years.

Conclusions. In the long term, manual therapy, including desensitization maneuvers of the central nervous system, resulted in similar outcomes and similar surgery rates compared with surgery in women with CTS. Both interventions were combined with a tendon/nerve gliding exercise program at home.

Impact. This is the first study to our knowledge to report clinical outcomes and surgical rates during a 4-year follow-up and will inform decisions regarding surgical versus conservative management of CTS.

Lay summary. Women with CTS may receive similar benefit from a more conservative treatment—manual therapy—as they would from surgery.

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Carpal tunnel syndrome (CTS) is considered the most common entrapment neuropathy of the upper extremity. The estimated incidence of CTS in the United States has been reported to be 542 per 100,000 in women.[1] Its prevalence rate ranges from 6.3% to 11.7%, depending on the definition of cases.[2] Since CTS affects middle-age active workers, it is associated with substantial health care costs and economic burden. For instance, the overall annual cost associated with CTS in the United States exceeds $2 billion.[3]

Conservative and surgical approaches are the therapeutic strategies most commonly applied for the management of CTS. Current guidelines recommend different interventions, such as orthoses, exercise, and manual therapy[4,5]; however, no consensus exists as to which option is more effective. In fact, surgery continues to be the treatment approach most commonly used for CTS,[6] although differences with conservative management are relatively smaller than expected.[7,8] Similarly, several trials investigating cost-effectiveness of conservative versus surgical approaches have found similar health care costs for both treatments, although the incremental cost-utility ratio is slightly favorable for surgery due to better outcomes in the surgery groups.[9,10]

It is important to note that most conservative treatments used for CTS, such as splinting, laser, and steroid injections, are mainly based on local approaches over the wrist. Fernández-de-las-Peñas et al have conducted a randomized controlled trial investigating the effects of an approach consisting of manual therapies including desensitization maneuvers of the central nervous system versus surgery in women with CTS and observed that this manual therapy approach obtained better short-term and similar long-term effects on pain intensity and related-function than surgery.[11] Similarly, a posterior economic analysis of the same trial showed that manual therapy was equally effective, but less costly, compared with surgery for CTS.[12] This randomized controlled trial provides promising results for the management of CTS, but long-term follow-up is clearly needed.

A review of the literature concluded that most studies on CTS only include a 1-year follow-up period.[13] Additionally, the same review also observed that, although surgery reported positive long-term results, the recurrence rate ranges from 5% to 57%.[13] Tang et al reported that individuals with bilateral severe CTS who received bilateral surgery exhibited positive results 9 years after the surgical procedure.[14] However, this was a prospective case series including individuals with severe bilateral CTS, which does not represent the general population of CTS cases. The recent systematic review conducted by Burton et al observed that most CTS patients (23%–89%) receiving conservative local treatments experienced negative outcomes at 3 years and that surgery rates after initial conservative management were as high as 60%.[15]

Therefore, the objectives of the current analysis were to investigate the 4-year effects of a manual therapy approach for CTS compared with carpal tunnel release surgery and to determine the recurrence rate of post-treatment carpal tunnel release surgery in the same cohort of women with CTS.[11]

Methods

Study Design

This study was a continuation of a randomized controlled trial with a 4-year evaluation end point,[11] performed in a general hospital in Spain, to evaluate the long-term effects of manual therapy including desensitization maneuvers targeting the central nervous system and compared with surgery in women with CTS. Full details of the trial, participants, interventions, and results of the outcomes at short- and mid-term follow-up periods are reported elsewhere.[11] The study was approved by the Hospital Universitario Fundación Alcorcón (HUFA) Institutional Review Board (PI01223-HUFA12/14), and the trial was prospectively registered (ClinicalTrials.gov: NCT01789645).

Participants

As previously described, women with clinical and electrophysiological findings of CTS were recruited from a local regional hospital in Spain.[11] Participants had to exhibit symptoms (eg, pain or paresthesia in the median nerve distribution), clinical signs (eg, Tinel/Phalen sign), and electrodiagnostic deficits of median nerve conduction according to the guidelines of the American Association of Electrodiagnosis, the American Academy of Neurology, and the American Physical Medicine and Rehabilitation Academy.[16] The 9 exclusion criteria were as follows: sensory/motor deficit in the ulnar or radial nerve; older than 65 years; previous hand surgery or steroid injection treatment; multiple diagnoses in the upper extremity; cervical and/or upper extremity trauma; any systemic disease causing CTS (eg, diabetes mellitus, thyroid disease); comorbid musculoskeletal pain conditions (eg, rheumatoid arthritis and/or fibromyalgia); pregnancy; and presence of depressive symptoms (Beck Depression Inventory-II score of >8 points). Participants signed an informed consent form prior to their inclusion.

Randomization and Masking

Patients were randomly assigned to receive manual therapy or surgery as previously described.[11] Briefly, concealed allocation was performed by using a computer-generated randomized table of numbers created by an external statistician not involved in other parts of the study. Individual and sequentially numbered index cards with the random assignment were prepared, folded, and placed in sealed opaque envelopes. A different researcher opened the envelope and proceeded with treatment allocation.

Due to the nature of the interventions (surgery vs manual therapy), it was not possible to mask therapists or patients. However, the clinician who collected follow-up data was masked with regard to group allocation.

Interventions

Participants allocated to the manual therapy group received 3 treatment sessions, once per week, of manual therapy consisting of desensitization maneuvers of the central nervous system for a duration of 30 minutes.[11] Briefly, the desensitization maneuvers included soft tissue mobilization techniques targeting anatomical-related sites of potential entrapment of the median nerve (eg, scalene, pectoralis minor, biceps brachii, pronator teres muscle), lateral glide mobilization of the cervical spine, and tendon/nerve gliding exercises.[11] As previously described, interfaces were examined by the clinician and then treated according to the following clinical findings: pain on palpation and reproduction of any of the patient's symptoms.[11] Manual therapy approaches included in the trial are described in Appendix 1. Patients also received an educational session on how to perform tendon and nerve gliding exercises as homework if necessary.

Patients randomly allocated to the surgery group underwent open or endoscopic release of the carpal tunnel. Since no evidence supports 1 particular surgical procedure, surgery was based on the preferences of surgeons and patients.[17]Additionally, patients allocated to this group received the same educational session for performing tendon/nerve gliding exercises as the manual therapy group.[11] The educational session and homework included a tendon/nerve gliding exercise, which was the same in both groups and is described in Appendix 2.

Outcomes

The primary outcome was the intensity of hand pain.[11] An 11-point numerical pain rating scale (0 = no pain and 10 = maximum pain) was used to determine the patients' current level of hand pain and the worst level of pain experienced in the preceding week. Since no minimal clinically important difference exists for hand pain, a change of 2 points or a 30% decrease in baseline score was considered as clinically relevant.[18]

Secondary outcomes included functional status and symptom severity subscales of the Boston Carpal Tunnel Questionnaire[19] and self-perceived improvement with the Global Rating of Change. Higher scores on the Boston Carpal Tunnel Questionnaire indicate worse function and greater symptom severity. The minimal clinically important differences have been determined to be 0.74 points for the function subscale and 1.14 points for the symptom severity subscale.[20] Within the Global Rating of Change, scores of +4 and +5 are indicative of moderate changes in patient's status, whereas scores of +6 and +7 indicate large changes. In the original trial, outcomes were assessed at baseline and 1, 3, and 6 months and 1 year after treatment.[11] The current analysis reports outcomes at baseline and 1 and 4 years after treatment. We also defined a successful outcome when at least 1 of the following items, based on their respective minimal clinically important differences, was present: a reduction of $\geq$0.74 point or 1.14 points, respectively, on the Boston Carpal Tunnel Questionnaire function or symptom severity subscale[20] or a decrease of $\geq$2 points or a 30% reduction from baseline scores in the intensity of hand pain.[18]

In the current follow-up analysis, we also assessed the rate of surgical interventions (first in the manual therapy group or repeat surgery in the surgical group) during all follow-up periods. Finally, participants were also asked if they received other conservative treatments during the 4-year follow-up period.

Data Analysis

Sample size was initially calculated for detecting clinical changes in the intensity of hand pain at 1-year follow-up.[11] Statistical analysis was performed using SPSS software (Version 22.0, SPSS, Chicago, IL, USA) conducted according to the intention-to-treat principle for patients in the group to which they were originally allocated. Missing data were estimated using multiple imputations. Since this long-term follow-up analysis is non-inferiority testing, a per-protocol analysis was also conducted (data not shown) to determine convergent findings with both approaches (intention-to-treat vs per-protocol). Descriptive statistics were used to describe participants' features at baseline in both groups and can be found in the original report of the trial.[11] Our evaluation included mixed-model repeated-measured analyses of covariance with time as the within-subject factor and group as the between-subject factor and adjusted for baseline scores for detecting between-group differences in all outcomes at 1- and 4-year follow-up periods. To enable comparison of effect sizes, standardized mean differences (MDs) were calculated by dividing the between-group difference mean score by the pooled SD, if significant differences are observed. We also used chi-square tests to compare self-perceived improvement, as assessed with the Global Rating of Change, and success rates at 1- and 4-year follow-up periods in both groups. Finally, chi-square tests were also used for detecting between-group differences within surgical intervention rate and the use of other conservative treatments during the 4-year follow-up period.

Role of the Funding Source

The sponsor had no role in the design, collection, management, analysis, or interpretation of the data, draft, review, or approval of the manuscript or its content. The authors were responsible for the decision to submit the manuscript for publication, and the sponsor did not participate in this decision.

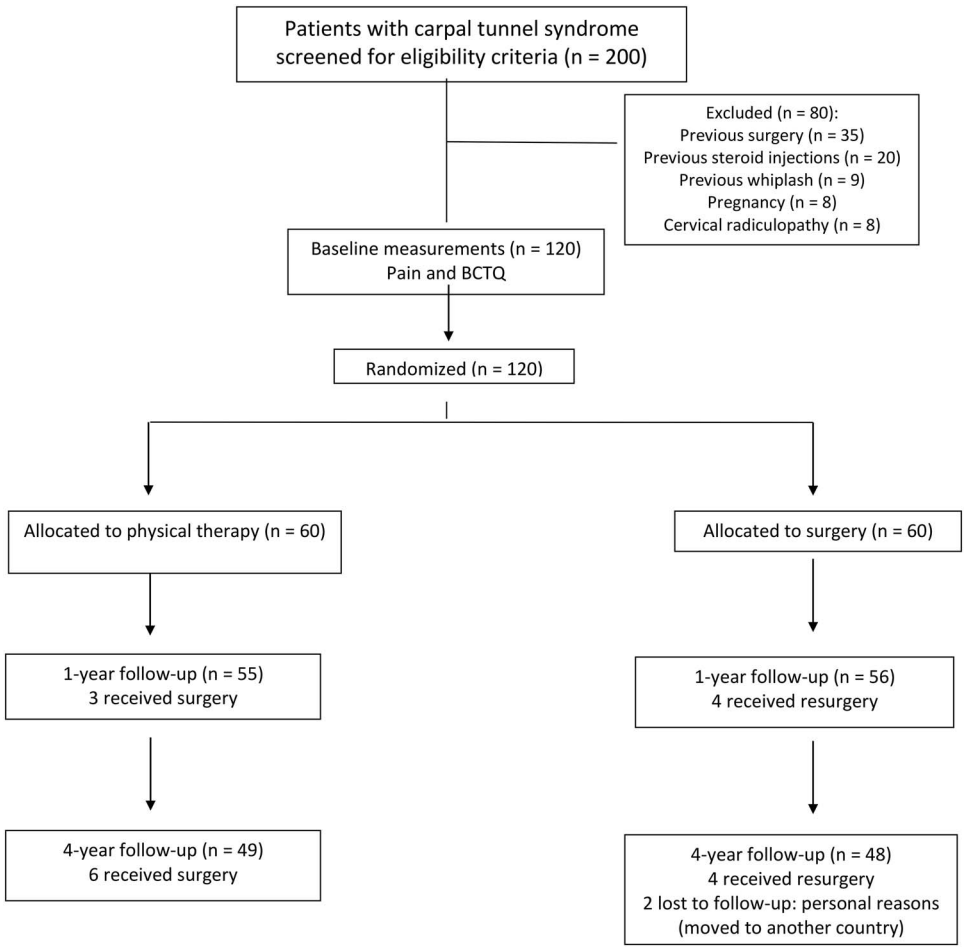

Figure 1.
Flow diagram of participants from randomization to 4-year follow-up by intention-to-treat (ITT).

Patient and Public Involvement

Patients were not involved in the study design, but they actively participated in the trial during the intervention period because they were asked for a home exercise program, if needed.

Results

Participants

From a total of 120 patients initially included in the original trial and randomly allocated into manual therapy (n = 60) or surgery (n = 60), 111 (92.5%) completed the 1-year[11] and 97 (81%) completed the 4-year follow-up main analysis. The flow diagram of participants during the trial leading to the 4-year follow-up period is shown in Figure 1. As previously described, original baseline variables did not differ between the groups.[11] Similarly, baseline scores of the final sample (n = 97) included in the 4-year analysis did not significantly differ (Tab. 1). No significant differences (all *P*s > .439) were found on demographic or clinical baseline data between patients who completed the study (n = 97) and those who did not (n = 23).

Changes in Pain and Function

As previously reported,[11] patients receiving manual therapy exhibited higher decreases at 1 and 3 months in mean pain intensity and higher decreases at 1, 3, and 6 months in the worst pain intensity than those receiving surgery (Fig. 2). The main results of the current analysis revealed no significant (all *P*s > .2) between-group differences at 1 year (mean pain: MD = −0.3, 95% CI = −0.9 to 0.3; worst pain: MD = −1.2, 95% CI = −3.6 to 1.2; function: MD = −0.1, 95% CI = −0.4 to 0.2; symptom severity: MD = −0.1, 95% CI = −0.3 to 0.1) and 4 years (mean pain: MD = 0.1, 95% CI = −0.2 to 0.4; worst pain: MD = 0.2, 95% CI = −0.8 to 1.2; function: MD = 0.1, 95% CI = −0.1 to 0.3; symptom severity: MD = 0.2, 95% CI = −0.2 to 0.6). Table 2 shows baseline, 1-year, and 4-year data for pain and function outcomes.

Table 1.
Baseline Characteristics by Treatment Assignment of the Sample Included at the 4-Year Follow-up[a]

Characteristic	Physical Therapy Group (n = 49)	Surgery Group (n = 48)
Age, y	47 (10)	48 (8)
Years with pain	3.6 (2.8)	3.9 (2.0)
Occupation[b]		
Work at home	25 (51)	24 (50)
Secretary/office	24 (49)	24 (50)
Unilateral/bilateral arm distribution[b]		
Unilateral symptoms, right side	6 (12)	8 (17)
Unilateral symptoms, left side	3 (6)	2 (4)
Bilateral symptoms	40 (82)	38 (79)
Severity[b]		
Minimal CTS	13 (26)	10 (21)
Moderate CTS	19 (39)	24 (50)
Severe CTS	17 (35)	14 (29)
Mean intensity of pain (NPRS score = 0–10)	4.8 (1.5)	4.9 (2.1)
Worst pain experienced last week (NPRS score = 0–10)	6.7 (1.7)	6.9 (2.0)
Functional status for CTS (BCTQ score = 1–5)	2.3 (0.5)	2.4 (0.6)
Severity status for CTS (BCTQ score = 1–5)	2.5 (0.7)	2.7 (0.7)
BDI-II (score = 0–21)	3.7 (2.6)	4.0 (2.3)

[a] Data are reported as mean (SD) unless otherwise indicated. BCTQ = Boston Carpal Tunnel Questionnaire; BDI-II = Beck Depression Inventory-II; CTS = carpal tunnel syndrome; NPRS = numerical pain rating scale.
[b] Data are reported as number (percentage) of participants.

Table 2.
Primary and Secondary Outcomes at Baseline, 1 Year, and 4 Years by Randomized Treatment Assignment[a]

Parameter	Outcome Group	Baseline	1 y	4 y
Mean level of hand pain (NPRS score = 0–10)	Physical therapy	4.8 (4.3–5.3)	1.4 (1.0–1.8)	2.3 (1.7–2.9)
	Surgery	4.9 (4.4–5.4)	1.7 (1.2–2.2)	2.2 (1.5–2.9)
Worst level of hand pain experienced in preceding week (NPRS score = 0–10)	Physical therapy	6.7 (6.1–7.3)	2.0 (1.2–2.8)	4.0 (3.3–4.7)
	Surgery	6.9 (6.3–7.5)	3.2 (2.5–3.9)	3.8 (3.0–4.6)
Function subscale of BCTQ (score = 1–5)	Physical therapy	2.3 (2.1–2.5)	1.5 (1.3–1.6)	1.5 (1.3–1.7)
	Surgery	2.4 (2.2–2.6)	1.6 (1.4–1.8)	1.4 (1.2–1.6)
Severity subscale of BCTQ (score = 1–5)	Physical therapy	2.5 (2.3–2.7)	1.5 (1.4–1.6)	1.7 (1.5–1.9)
	Surgery	2.7 (2.5–2.9)	1.6 (1.4–1.8)	1.5 (1.3–1.7)

[a] Data are expressed as mean (95% CI). BCTQ = Boston Carpal Tunnel Questionnaire; NPRS = numerical pain rating scale.

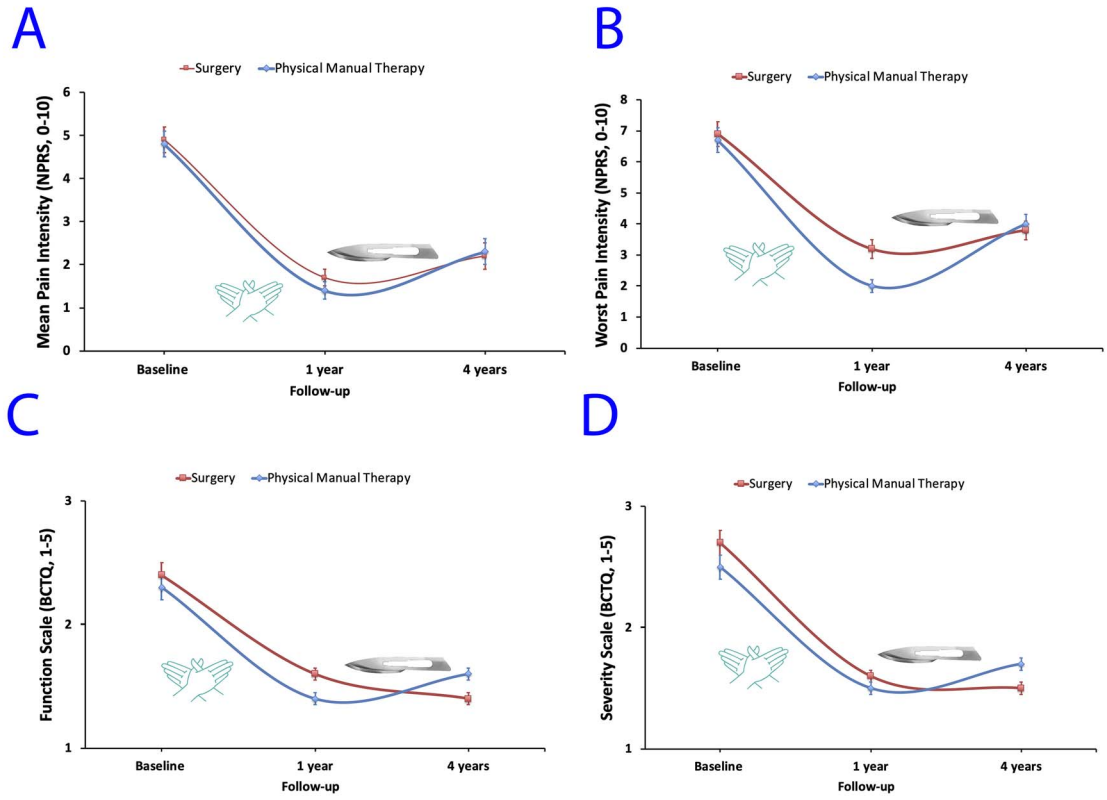

Figure 2.
Evolution of all outcomes (pain on the numerical pain rating scale [NPRS] [A and B] and Boston Carpal Tunnel Questionnaire [BCTQ] [C and D]) throughout the course of the study stratified by randomized treatment assignment. Data are means (SEs).

Self-Perception of Improvement

Manual therapy and surgical groups did not significantly differ on success criteria in the intention-to-treat analyses at 1 ($P > .264$) and 4 ($P > .288$) years (Tab. 3). Self-perceived improvement assessed with the Global Rating of Change was also similar at 1 ($P = .169$) and 4 ($P = .242$) years after treatment in both groups (Tab. 3).

Surgery Rate and Other Conservative Treatments

No significant between-group differences in surgery rate were found ($P = .448$) during the 4-year follow-up period. In patients originally allocated to the manual therapy group, 9 (15%) received surgery, 3 before the 1-year follow-up period, and the remaining 6 during the 4-year period. Similarly, in patients allocated to the surgery group, 4 received surgery or repeat surgery during the 1-year follow-up and another 4 during the 4-year follow-up (Fig. 1). No significant differences within the time frame from which patients received their first-time surgery (manual therapy group: 1.6 [SD = 1] years) or their repeat surgery (surgery group: 1.8 [SD = 0.7] years) intervention were observed.

No significant differences ($P = .270$) existed in the number of patients allocated to the manual therapy who seek and received other conservative intervention during the 4-year follow-up (n = 12, 24.5%) versus those allocated to the surgery group (n = 16, 33%). These participants reported that they have sporadically attended physical therapy for their pain.

Discussion

The current randomized controlled trial found that manual therapy consisting of manual therapies including desensitization maneuvers of the central nervous system and surgery combined with a tendon and nerve gliding exercise program at home resulted in similar outcomes on pain and function in women with CTS at 1- and 4-year follow-up periods. Similarly, self-perceived improvement, post-intervention surgical rate, and other conservative interventions received were also similar in both groups.

To our knowledge, this is the first randomized controlled trial investigating the effects of manual therapy in CTS at a follow-up of 4 years.[4,7,8,13] Our data indicate that both interventions seem to be equally effective long term since all outcomes demonstrated similar changes at 1 year and

Table 3.
Follow-Up Self-Perceived Recovery and Successful Outcomes in Surgical and Manual Therapy Groups[a]

Parameter	1-y Follow-Up [11]		4-y Follow-Up	
	Physical Therapy Group (n = 55)	Surgery Group (n = 56)	Physical Therapy Group (n = 49)	Surgery Group (n = 48)
Self-perceived improvement on the Global Rating of Change (−7 to +7)				
Moderate changes				
+4	7 (13)	10 (18)	4 (8)	4 (8)
+5	15 (27)	12 (21)	5 (10)	5 (10.5)
Large changes				
+6	5 (9)	17 (30)	9 (18)	8 (16.5)
+7	12 (22)	13 (23)	19 (39)	16 (33)
Successful outcomes (≥0.6 point or ≥1.14 points on the BCTQ for function or severity, respectively, or ≥2 points on the NPRS or 30% improvement in pain intensity)[b]				
One criterion	44 (76)	50 (83)	31 (63)	32 (67)
All criteria	31 (53)	27 (45)	22 (45)	21 (44)

[a] Data are reported as number (percentage) of participants. BCTQ = Boston Carpal Tunnel Questionnaire; NPRS = numerical pain rating scale.
[b] For physical therapy at 1-year follow-up, n = 58; for surgery at 1-year follow-up, n = 60.

4 years. Nevertheless, changes in the manual therapy group on the worst pain experienced the previous week exhibited a potential trend for worsening (from 2.0 to 4.0 points) to a greater extent compared with the surgery group (from 3.2 to 3.8), although it was not significantly different and only occurred in this outcome. The clinical relevance of this trend should be investigated in the context of a 4-year follow-up period. An important finding was that only 15% of those women who received manual therapy required surgery 4 years after the intervention. This is contrary to previous findings suggesting a surgery rate of 60% after localized conservative treatment.[15] Current data may be related to a clinical reasoning underlying manual therapy used in this study. Previous studies examining the effectiveness of physical therapy versus surgery for CTS mainly used localized therapeutic approaches that solely target the wrist and/or hand, resulting in limited evidence.[4–10] These approaches are based on the traditional premise that CTS is considered as localized pathology just associated with a peripheral lesion at the carpal tunnel, but current evidence suggests that CTS is a complex disorder exhibiting sensitization mechanisms.[21,22] Therefore, the proposed manual therapy approach included soft tissue mobilizations and nerve/tendon gliding techniques directed at the entire upper extremity accordingly to current nociceptive theories on CTS.[23] Therefore, it seems that manual therapies including desensitization maneuvers of the central nervous system may be more effective than localized interventions targeting only the hand and/or the wrist in this population. Obviously, it is important to consider that both groups also received a tendon/nerve gliding exercise program as homework, which could also influence 1- and 4-year follow-up outcomes. Similarly, it is also difficult to determine the effects of the other conservative intervention used by patients during the 1- and 4-year follow-up periods; nevertheless, the use of other interventions was similar between groups and was sporadic.

Based on our results, the proposed conservative approach may be considered as a first-line treatment option for CTS before subsequently considering surgery. This proposal is in line with the fact that most patients typically prefer conservative management as the first therapeutic option because of the higher rate of complications associated with surgery. Nevertheless, there is evidence suggesting that outcomes are inferior if patients first receive conservative treatment instead of surgery.[24] Again, this assumption is based on an application of localized conservative treatments and not the current proposal based on nociceptive pain mechanisms. Current clinical guidelines propose the use of conservative treatments in mild to moderate, and sometimes severe, cases of CTS[4,5]; however, no consensus exists on which patients would better benefit from either conservative or surgical treatment. Therefore, identification of patients who will benefit from each intervention is needed.

The results of this randomized controlled trial should be considered according to the potential strengths and limitations. Strengths included the application of a manual therapy approach applying clinical reasoning based on current nociceptive theories of CTS and inclusion of different therapies (manual therapy vs surgery) in either treatment group, although both groups received the same

tendon/nerve gliding exercise program as homework. Further, we included a 4-year follow-up. Nevertheless, it should be recognized that we had a 20% loss to follow-up, but this was similar in both groups. In fact, loss to follow-up for most participants was due to surgery within the manual therapy group or repeat surgery within the surgery group, which was one of the objectives of this 4-year follow-up analysis. In fact, the per-protocol analysis revealed the same findings where there was no difference between groups for any of the outcomes.

Among the limitations, multicenter studies controlling for site and therapist effects in subsequent trials might enhance the generalizability of our results. Similarly, the strict inclusion and exclusion criteria used in this study could limit the generalizability of these results. Second, patients and clinicians were not blinded with regard to the treatment intervention due to the nature of the treatments. Third, we did not consider the role of psychological variables, such as mood disorders or sleep disturbances. Additionally, we did not reassess provocative tests used in the physical examination, such as the Phalen or Tinel test, or electromyographic data at any follow-up period, which could also elucidate potential between-group differences. Fourth, patients allocated to the manual therapy group received 3 sessions based on the author clinical experience since no available data exist on the frequency and dose of therapy. We do not know if a greater number of sessions would reveal differences between interventions, as it has been observed with the application of corticosteroid injections.[25] Fifth, only women with CTS were included. In addition, compliance with home exercises was not monitored and, hence, the influence of this co-intervention on long-term outcomes is unknown at this stage.

This randomized controlled trial found that manual therapy consisting of desensitization maneuvers of the central nervous system and surgery combined with a tendon and nerve gliding exercise program as homework resulted in similar outcomes in women with CTS at 4 years. Similarly, self-perceived improvement, post-intervention surgical rate, and other conservative interventions received were also similar between groups. Manual therapy can be considered a first-line treatment option for CTS as it is equally effective of surgery.

Author Contributions

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Providing institutional liaisons: C. Fernández-de-las-Peñas
Clerical/secretarial support: G. Plaza-Manzano
Consultation (including review of manuscript before submitting): C. Fernández-de-las-Peñas, J.L. Arias-Buría, J.A. Cleland, J.A. Pareja, G. Plaza-Manzano, R. Ortega-Santiago

Ethics Approval

This study was approved by the Hospital Universitario Fundación Alcorcón Institutional Review Board (PI01223-HUFA12/14).

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Clinical Trial Review Registration

This trial was prospectively registered at ClinicalTrials.gov (NCT 01789645).

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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Appendix 1. Description of Manual Therapy Interventions

Technique: Manual compression of the scalene muscles.

Description of Technique: The patient lies supine with the cervical spine in a neutral position. The therapist applied a manual pain-free compression over the anterior/middle scalene muscle for 1 minute (Suppl. Fig. 1).

Technique: Manual mobilization of the costoclavicular space.

Description of Technique: The patient was side-lying with the affected extremity up. The second and third fingers of the caudal hand of the therapist contacted the anterior part of the axilla, behind the pectoralis minor tendon. The thumb of the cranial hand contacted the superior part of the clavicle bone. The therapist applied a transverse mobilization for 1 minute (Suppl. Fig. 2).

Technique: Manual compression of the pectoralis minor muscle.

Description of Technique: The patient is side-lying with the affected extremity up with the shoulder abducted 90°. The therapist places the caudal hand over the rib cage behind the pectoralis minor muscle, and the cranial hand grasps the elbow of the patient. The therapist maintains a pain-free compression over the pectoralis minor muscle for 3 minutes (Suppl. Fig. 3).

Technique: Longitudinal stroke of the biceps muscle.

Description of Technique: The patient lies supine with the upper extremity relaxed, the elbow is extended, and the forearm supinated. The therapist applies 5 longitudinal strokes over the biceps brachii muscle from a cranial to caudal direction (Suppl. Fig. 4).

Technique: Manual mobilization of the bicipital aponeurosis.

Description of Technique: The patient lies supine with the shoulder abducted and the elbow flexed to 90°. The therapist grasps the bicipital aponeurosis (lacertus fibrosus) of the biceps brachii muscle with one hand. The other hand grasps the wrist of the patient and then rhythmically extends the elbow of the patient 10 times (Suppl. Fig. 5).

Technique: Manual mobilization of the pronator teres muscle.

Description of Technique: The patient lies supine with an extended elbow and the forearm in neutral. The cranial hand of the therapist palpates the pronator teres muscle. The caudal hand grasps the wrist. The therapist rhythmically pronates the forearm of the patient 10 times during this technique (Suppl. Fig. 6).

Technique: Manual mobilization of the transverse carpal ligament.

Description of Technique: The patient lies supine with the upper extremity relaxed. The therapist grasps the wrist of the patient with the thumbs on the region of the carpal tunnel. The remaining flexed index fingers are placed over the back of the wrist. The therapist rhythmically provides an extension movement of the wrist 10 times (Suppl. Fig. 7).

Technique: Manual stretching of the palmar aponeurosis.

Description of Technique: The patient lies supine with the elbow flexed to 90°. The therapist grasps all the fingers by opening the hand of the patient. The therapist induces an opening motion of the fingers with slight wrist extension for 10 repetitions (Suppl. Fig. 8).

Technique: Manual mobilization of lateral glide of the cervical spine.

Description of Technique: The patient lies supine with the cervical spine in neutral. The caudal hand of the therapist supports the patient's mid-cervical spine at the C5/C6 level. The cranial hand of the therapist is placed on the contra-lateral side of the neck of the patient. A lateral glide of the cervical spine was applied as a translational movement of the neck away from the symptomatic side. The intervention was completed over 5 minutes in 2 sets of 2 minutes each with 1 minute rest between sets (Suppl. Fig. 9).

Technique: Tendon/nerve gliding exercise targeting the median nerve.

Description of Technique: The patient was supine with the cervical spine in neutral. This tendon/nerve gliding exercise was performed by alternating the following positions of the upper extremity: 1, shoulder girdle depression, glenohumeral abduction and lateral rotation, forearm supinated, elbow flexed, and wrist/thumb/and fingers extension (Suppl. Fig. 10); 2, shoulder girdle depression, glenohumeral abduction/lateral rotation, forearm supinated, elbow extended, and wrist/thumb/fingers flexion (Suppl. Fig. 11). The exercise was completed in 2 sets of 10 repetitions min each with 1 minute rest between sets.

Appendix 2. Guideline for Tendon/Nerve Gliding Exercises for Home

All participants received an educational session where the therapist explained the effects and potential benefits of tendon/nerve gliding exercises for their pain condition on how performing the exercises as homework, if needed. The therapist explained the following tendon/nerve gliding exercises:

Exercise 1: The patient places the affected upper extremity in elbow flexion and wrist extension for 30 seconds (Suppl. Fig. 12).

Exercise 2: The patient places the affected upper extremity in elbow extension and wrist in neutral or in flexion for 30 seconds (Suppl. Fig. 13).

Exercise 3: If possible, the patient places the affected upper extremity with both elbow and wrist extension for 30 seconds (Suppl. Fig. 14).

Exercise 4: The patient was prescribed a "slider" technique targeted the median nerve. The patient alternates the following sequence: 1, glenohumeral abduction and external rotation, forearm supinated, elbow flexed, and wrist/thumb/and fingers extension with the cervical spine in neutral position (Suppl. Fig. 15); 2, from the same position the patient increases elbow flexion and at the same time the cervical spine goes into contra-lateral side-bending (Suppl. Fig. 16); 3, from the same position the patient puts elbow extension and at the same time the cervical spine goes into homo-lateral side-bending towards the symptomatic side (Suppl. Fig. 17). The sequence was repeated 5 times, if conducted.

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REVIEW

The effectiveness of manual therapy on pain, physical function, and nerve conduction studies in carpal tunnel syndrome patients: a systematic review and meta-analysis

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Abstract

Aim of the study Systematic review and meta-analysis to assess the effectiveness of manual therapy in improving carpal tunnel syndrome (CTS) symptoms, physical function, and nerve conduction studies.

Method MEDLINE, Web of Science, SCOPUS, Cochrane Library, TRIP database, and PEDro databases were searched from the inception to September 2021. PICO search strategy was used to identify randomized controlled trials applying manual therapy on patients with CTS. Eligible studies and data extraction were conducted independently by two reviewers. Methodology quality and risk of bias were assessed by PEDro scale. Outcomes assessed were pain intensity, physical function, and nerve conduction studies.

Results Eighty-one potential studies were identified and six studies involving 401 patients were finally included. Pain intensity immediately after treatment showed a pooled standard mean difference (SMD) of − 2.13 with 95% confidence interval (CI) (− 2.39, − 1.86). Physical function with Boston Carpal Tunnel Syndrome Questionnaire (BCTS-Q) showed a pooled SMD of − 1.67 with 95% CI (− 1.92, − 1.43) on symptoms severity, and a SMD of − 0.89 with 95% CI (− 1.08, − 0.70) on functional status. Nerve conduction studies showed a SMD of − 0.19 with 95% CI (− 0.40, − 0.02) on motor conduction and a SMD of − 1.15 with 95% CI (− 1.36, − 0.93) on sensory conduction.

Conclusions This study highlights the effectiveness of manual therapy techniques based on soft tissue and neurodynamic mobilizations, in isolation, on pain, physical function, and nerve conduction studies in patients with CTS.

Keywords Carpal tunnel syndrome · Manual therapy · Median nerve · Neuropathies · Meta-analysis

Sandra Jiménez-del-Barrio and Aida Cadellans are equall contribution.

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Introduction

Carpal tunnel syndrome (CTS) is considered the result of the compression of the median nerve in the carpal tunnel [1, 2] and is one of the most common upper extremity neuropathies [3–5]. Recent studies show that CTS's prevalence and the incidence are increasing in the last years [6, 7], causing important socioeconomic cost [4]. Patients with CTS often report pain, paraesthesia, sensory disturbances, weakness in the hand and wrist, causing a physical function decrease that affects daily living activities [8, 9]. Due to the high prevalence of CTS, its effects on daily living activities and the health care cost are necessary to identify the best therapeutic approaches [4]. Secondary causes have been described of CTS including traumatism, metabolic conditions, infections, neuropathies, or other systemic disorders. However, most of cases of CTS are idiopathic [4, 5].

Clinical guidelines recommend conservative treatment to manage symptoms and loss of function of patients with mild to moderate CTS [10]. The leading conservative treatments are splinting, steroid injection, electrotherapy, and manual therapy [11, 12]. Manual therapy applied on CTS patients includes different interventions such as manual and instrumental soft tissue mobilizations, massage therapy, bone mobilizations or manipulations, and neurodynamic techniques, focused on skeletal system or soft tissue [13]. As previous studies suggested, when the CTS has not a clear cause, the manual therapy applications could reduce the epineural tethering in the forearm and could improve the nerve gliding in the carpal tunnel during the movement of the wrist, fingers, or elbow. The number of studies analyzing manual therapy interventions has increased in last years, and they have shown positive effects on symptoms and physical function in patients with CTS [14–20]. Although a recent review has assessed the effects of conservative treatments in patients with CTS [21], to the best of our knowledge, no systematic review with meta-analysis has been performed in order to assess the effectiveness of manual therapy on the main symptoms, function, and nerve conduction studies in patients with CTS [22, 23].

The aim of this systematic review and meta-analysis was to assess the effectiveness of manual therapy qualitatively and quantitatively in improving CTS symptoms such as pain, physical function, and nerve conduction studies.

Methods

A systematic review of the scientific literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement checklist and the Guidelines of Cochrane Handbook for Systematic Reviews of Interventions Version 6 was conducted [24]. The study was registered in the PROSPERO with the following registration number CRD42020167559.

The PICO strategy was developed in order to perform an accurate search strategy. Population were patients diagnosed with CTS; intervention studied was manual therapy techniques applied in isolation; comparison was control, placebo, sham, or simulated intervention; main outcomes were pain intensity, functionality, disability, and nerve conduction studies. Keywords used to develop the search strategy are shown on Table 1.

MEDLINE, Web of Science, SCOPUS, Cochrane Library, TRIP database, and PEDro were the databases used for the computerized search strategy. The last search was performed on September 1, 2021. The strategy was modified and adapted for each searched database with no restriction of language. Reference list of the included studies and the relevant reviews were also manually screened to identify additional studies for inclusion. Search strategies used are available in Appendix 1.

Studies were eligible if they met the following criteria: (1) randomized controlled trial design, (2) patients diagnosed with CTS, (3) manual therapy techniques applied in isolation, (4) compared to control, sham, simulated or placebo intervention, (5) studies measuring pain intensity, functionality, disability,

Table 1 Keywords used for the search strategy

Population	Intervention	Control	Outcomes
Carpal tunnel syndrome	Manual therapy Neurodynamic Neural mobilization Graston Neural tension Mobilization Manipulation Massage Fibrolysis Diacutaneous Surgery Surgical Resease	Control Placebo Sham Simulated	Symptom* Functi* Nerve conduction studies Functional capacity Disability Ability Pain

and nerve conduction studies. Studies were excluded if any of the following criteria were met: (1) case reports, non-randomized controlled trials, reviews, crossover trial, (2) the procedure of the intervention was unspecified, (3) the treatment consisted of surgical procedures, (4) numerical data results were not provided. Two independent reviewers selected the studies by reading the title, abstract, and full texts. Any discrepancies were solved by a third independent reviewer.

Data collected for studies included in the present review was used to describe the study characteristics table (Table 2). Data extracted were the following: (1) author's last name (2) year; (3) study design; (4) sample size, gender, and mean age; (5) pathology; (6) control group intervention; (7) experimental group intervention; (8) outcome measures and tool used; (9) main results.

In order to assess the methodology quality and risk of bias of studies included in this systematic review, Physiotherapy Evidence Database (PEDro) scale was used (Table 3). It was assessed independently by two authors and a third author intervened in case of disagreement. The PEDro scale is an 11-item scale that relates the external validity, and the internal validity of a study. One point is awarded if the criteria is clearly satisfied as assessed by following cut-points 9–10: excellent; 6–8: good; 4–5: fair; < 4: poor.

RevMan 5.3 software package was used to develop all statistical analysis based on mean scores and standard deviation. Intervention effects were assessed by introducing changes between the baseline and the post-intervention assessment, comparing manual therapy group versus control group, provided on each study. If no post-intervention mean differences and standard deviation were provided by the authors, it was calculated by SPPS.

Standard mean difference (SMD) effect was used for all continuous outcomes because different scales and units were used in the main outcomes assessed. Random effects were used and the heterogeneity was assessed visually by means of forest plots and by reporting the I^2 statistic (low, moderate, or high if I^2 statistic was < 25%, 25–75%, or > 75% respectively). Pooled SMD and 95% confidence interval were calculated. If heterogeneity is considered significant > 70 I^2, sensitivity analysis was conducted. Funnel plots were used to illustrate the risk of publication bias.

Results

The search strategy generated a total of 532 studies that were potentially eligible for this review. Analysis of Cohen's Kappa index showed a $k = 0.48$ categorized as moderate agreement. Finally, six studies were included in the qualitative and quantitative synthesis. Figure 1 shows the PRISMA flowchart with the study selection procedure.

Characteristics of the studies included in this systematic review and meta-analysis are shown in Table 2. Studies involved 401 patients (52 males and 349 females) with CTS mean age ranged from 44.97 to 54.2 years. Three studies applied neurodynamic mobilizations based on sliding and tensioning neurodynamic techniques, two studies applied the diacutaneous fibrolysis technique and one study applied a myofascial stretching approach.

All studies included in this systematic review and meta-analysis measured pain intensity. Four studies considered function and five assessed nerve conduction.

Other outcomes measured in the studies but not related to this systematic review were grip pinch, range of movement or upper limb tension test.

The methodological quality assessed by PEDro scale indicated an overall high quality of the studies included in this systematic review. Five of the six studies scored between 8 and 11 with an average of 8.6 [15, 25–28]. Only one study scored a lower score of 6/11 on the scale [14]. The principal bias found between all studies was that there was not blinding of therapist who administered the therapy. However, due to the nature of the manual therapy techniques, it is not possible to completely blind therapist. Another common feature found was that results were not presented for all subjects initially included, due to the follow-up loses. Furthermore, in those cases, the data were not analyzed on an "intention to treat" basis.

Six studies were included on the quantitative synthesis. Pain, function, and nerve conduction outcomes were tested under the manual therapy versus a control therapy comparison for this meta-analysis. Only the immediate effects after technique application could be evaluated.

The study by Tel-Akabi et al. (2000) did not provide data for standard deviation but provided data for all patients ($n = 7$), so calculation could be performed.

Pain

The pain intensity effects immediately after manual therapy techniques were tested in all studies included (Fig. 2). Two hundred eighteen participants were included in the manual therapy groups and a hundred ninety-seven in the control group. Four of the five studies included used the visual analog scale (mm) for the pain assessment [14, 15, 26, 28], whereas the two other used the pain rating scale (from 0 to 10) [25, 27]. Pain intensity showed a pooled SMD (95% CI) of − 2.13 (− 2.39, − 1.86). Heterogeneity analysis by I^2 characteristics showed a high heterogeneity (96%). To detect whether any of the studies might have a greater influence on the heterogeneity results, a sensitivity test was performed by repeating the meta-analysis excluding one study at a time. We observed that removing any study heterogeneity and results did not notably decrease.

Table 2 Study characteristics

Population						Intervention					
Author (year)	Study design	*N*	Gender	Mean age	Pathology	Control/placebo/sham group	Intervention group	Comparative intervention group	Outcomes (tool)	Follow-up	Main results
Wolny et al. 2019 [27]	RCT	103 (58/45)	11/92	54.6 (9.1)/53.1 (10.1)	CTS	No intervention	NDS Three series of 60 repetitions of sliding and tensioning neurodynamic techniques separated by interseries intervals of 15 s 2/weeks (total: 20 sessions/10 weeks)		Pain intensity (NPRS) Function (BCTS-Q SSS) Function (BCTS-Q FSS) Nerve conduction (SCV) Nerve conduction (MCV) Nerve conduction (MT)	Before and after technique. (10 weeks)	↑ Pain, function, and nerve conduction
Wolny et al. 2018 [25]	RCT	150 (78/72)	15/135	54.2 (9.48)/52.2 (10.4)	CTS	Placebo therapy 3 series of 60 repetitions of placebo glide and tension neurodynamic techniques separated by interseries intervals of 15 s 2/week for 20 sessions (20 sessions/10 weeks)	NDS 3 series of 60 repetitions of glide and tension neurodynamic techniques separated by interseries intervals of 15 s 2/week (total: 20 sessions/10 weeks)		Pain intensity (NPRS) Function (BCTS-Q SSS) Function (BCTS-Q FSS) Nerve conduction (SCV) Nerve conduction (MCV) Nerve conduction (MT)	Before and after technique. (10 weeks)	↑ Pain, function, and nerve conduction
Jiménez-del-Barrio et al. 2018 [15]	RCT	52 (24/27)	11/41	44.97 (9.34)/48.83 (7.98)	CTS	Sham therapy 5 sessions All intervention lasted an average of 17.77 days (SD: 0.8) with an interval of two to five days between each session	DF 5 sessions All intervention lasted an average of 17.77 days (SD: 0.8) with an interval of two to five days between each session		Pain intensity (VAS) Nerve conduction (DML) Nerve conduction (SCV)	Before and after treatment, and one moth-follow-up	Posttreatment: ↑ pain and nerve conduction one month follow-up: ↑ pain

Table 2 (continued)

Population						Intervention					
Author (year)	Study design	*N*	Gender	Mean age	Pathology	Control/placebo/ sham group	Intervention group	Comparative intervention group	Outcomes (tool)	Follow-up	Main results
Jiménez-del-Barrio et al. 2021 [26]	RCT	39 (18/21)	5/34	45.5 (9.6)/49.6 (7.6)	CTS	Sham therapy 5 sessions All intervention lasted an average of 17.77 days (SD: 0.8) with an interval of two to five days between each session	DF 5 sessions All intervention lasted an average of 17.77 days (SD: 0.8) with an interval of two to five days between each session		Pain intensity (VAS) disability (BCTS-Q) nerve conduction (SCV)	Before and after treatment	↑ VAS nad nerve conduction
	RCT	21 (7/7/7)	0/21	47.1 (S.D. 14.8)	CTS	No intervention	Neurodynamic mobilization ULTT2a mobilization	Bone mobilization carpal bone mobilization (posterior-anterior and/ or anterior–posterior mobilization techniques) and flexor retinaculum stretch	Pain intensity (VAS) Function (PRS) Function (FBS)	Before and after treatment	↑ Pain and function
Shem etal. 2020 [28]	RCT	36 (17/19)	10/26	48.18 (7.18)/50.05 (9.71)	CTS	Sham therapy 30 s at a time, four times a day for six weeks	Self-myofascial stretching of the carpal ligament 30 s at a time, four times a day for six weeks		Pain intensity (VAS) Function (BCTS-Q FSS) Function (BCTS-Q SSS) Nerve conduction (sensory DL) Nerve conduction (motor DL)	Before and after treatment	↑ Pain and nerve conduction

RCT, randomized controlled trial; *CTS*, carpal tunnel syndrome; *NDS*, neurodynamic mobilizations; *DF*, diacutaneous fibrolysis; *VAS*, visual analog scale; *DL*, distal latency; *SCV*, sensory conduction velocity; *MCV*, motor conduction velocity; *DL*, distal latency; *BCTS-Q*, Boston Carpal Tunnel Syndrome Questionnaire

Table 3 PEDro scale

PEDro score	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total
Jiménez et al. 2018 [18]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	9
Jiménez et al. 2021 [26]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	10
Wolny et al. 2018 [25]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	9
Wolny et al. 2019 [27]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	9
Tal-Akabi et al. 2000 [14]	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	6
Shem et al. 2020 [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	9

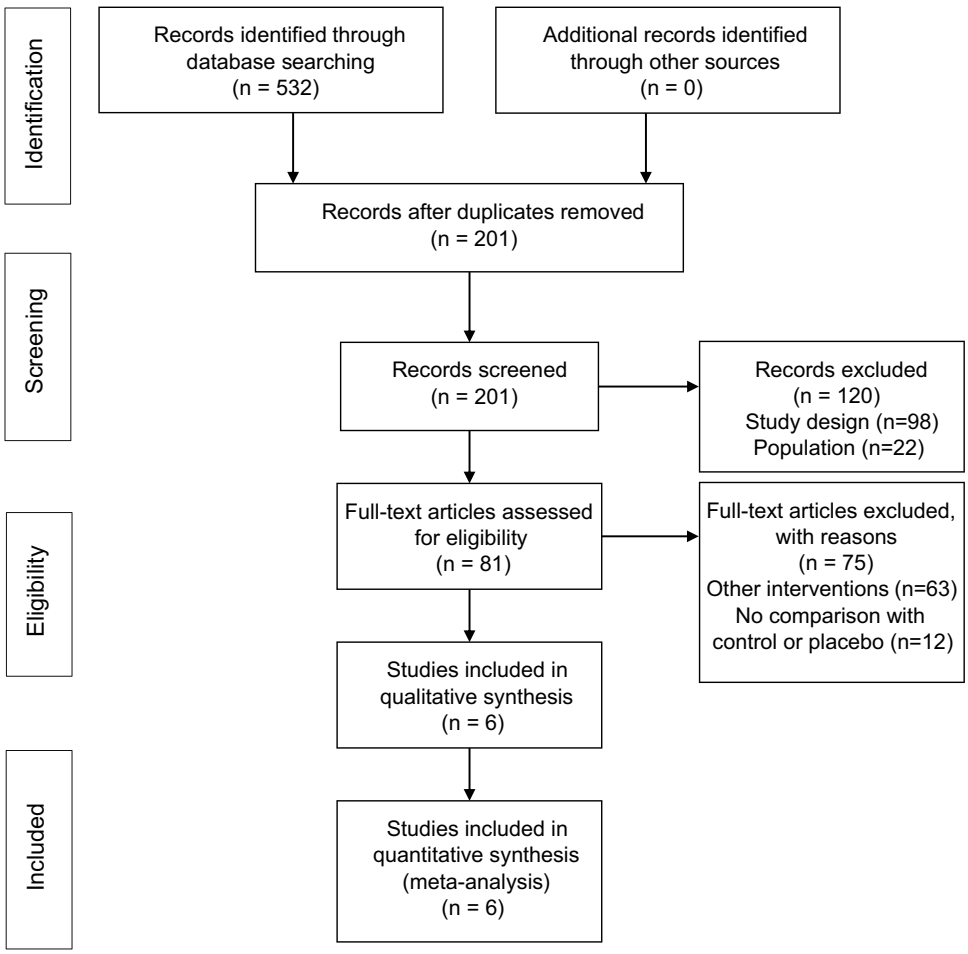

Fig. 1 PRISMA flow diagram

Function

Function outcome was assessed by means of the Boston Carpal Tunnel Syndrome Questionnaire (BCTS-Q) in all the studies included for this meta-analysis. This scale is sub-divided into two dimensions. One dimension focuses on the implication of symptom severity on functional tasks (Symptom Severity Scale), involving 11 items (Fig. 3), and the other one on function status properly (Functional Status Scale), involving 8 items (Fig. 5). However, not all studies provided data for both dimensions. Thus, the meta-analysis was conducted separately for each sub-scale.

All studies assessed function by means of symptom severity scale (BCTS) immediately after treatment [14, 15, 25,

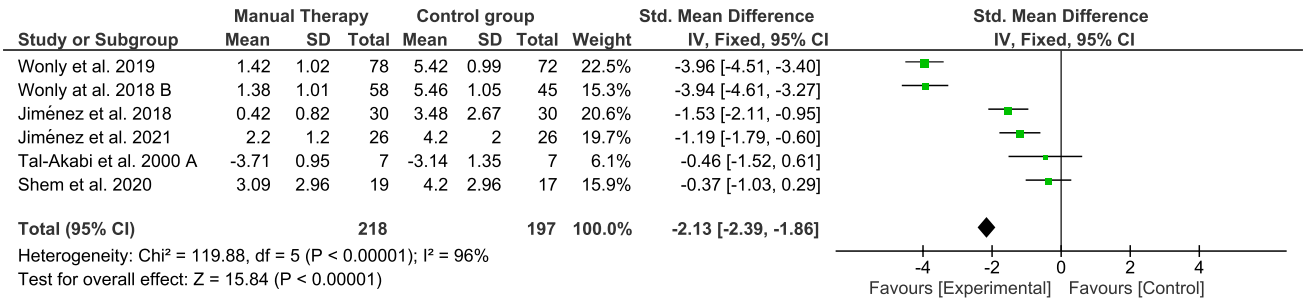

Fig. 2 Forest plot of comparison. Manual therapy vs control group. Outcome: pain

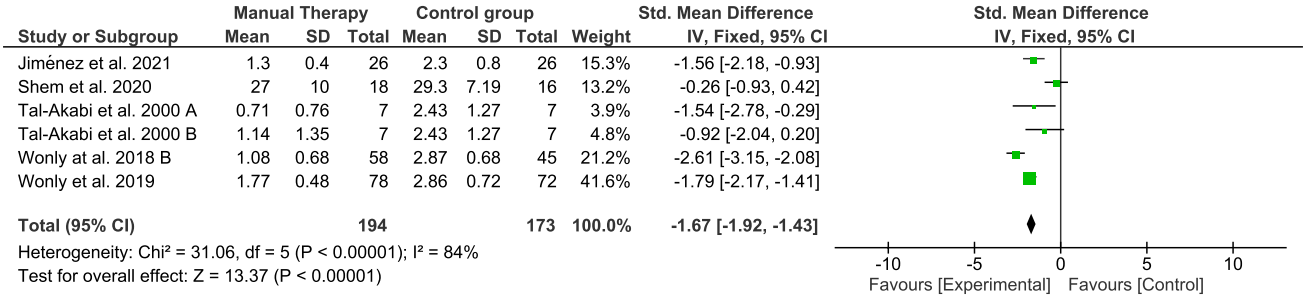

Fig. 3 Forest plot of comparison. Manual therapy vs control group. Outcome: symptom severity scale (BCTS-Q)

27, 28]. A hundred ninety-four participants were involved in the manual therapy groups and a hundred seventy-three in the control group. Function changes showed a pooled SMD (95% CI) of − 1.67 (− 1.92, − 1.43). Analysis by I^2 characteristics showed a high heterogeneity (84%) sensitivity analysis showed that removing Shem et al. (2020) [28] study may decrease the heterogeneity to moderate, which indicates. However, the SMD did not notably change after repeating the meta-analysis without this study.

On the other hand, four of the studies included in this meta-analysis provided data about functional status scale of BCTS [14, 25, 28]. Two hundred ninety-three participants were included in the manual therapy groups and two hundred and thirty-eight in the control group. Analysis showed a pooled SMD (95% CI) of − 0.89 (− 1.08, − 0.70). Heterogeneity analysis by I^2 characteristics showed a high heterogeneity (94%). Removing any study for sensibility analysis, heterogeneity and results did not notably change.

Nerve motor conduction

The nerve motor conduction was tested immediately after treatment in four studies included in this systematic review (Fig. 5). A hundred eighty-five participants were involved in the manual therapy group and a hundred sixty-four in the control group. Four studies provided data of nerve motor conduction by nerve conduction studies, two obtained latencies [15, 28] and two motor conduction velocity and distal motor latency [25, 27] by nerve conduction studies. Nerve conduction showed a pooled SMD (95% CI) of − 0.19 (− 0.40, − 0.02). Heterogeneity analysis by I^2 characteristics showed a moderate heterogeneity (69%). Removing Jiménez et al. (2018) [15] study, for the sensitivity analysis showed that I^2 drops to 0%, which may indicate that without this study, the homogeneity would be almost perfect. However, when repeating the meta-analysis without it, the results were not notably modified.

Nerve sensory conduction

The nerve sensory conduction was assessed in five studies included in this systematic review (Fig. 6). Two hundred eleven participants were part of the manual therapy group and a hundred ninety of the control group. Five studies provided data of sensory conduction velocity by nerve conduction studies [15, 25–28]. Nerve conduction showed a pooled SMD (95% CI) of − 1.15 (− 1.36, − 0.93). Moderate heterogeneity was observed in I^2 (75%). The sensitivity analysis indicated that the study of Shem et al. (2020) significantly contributed to this value because the heterogeneity dropped to 0% when was excluded. Likewise, the results did not significantly change.

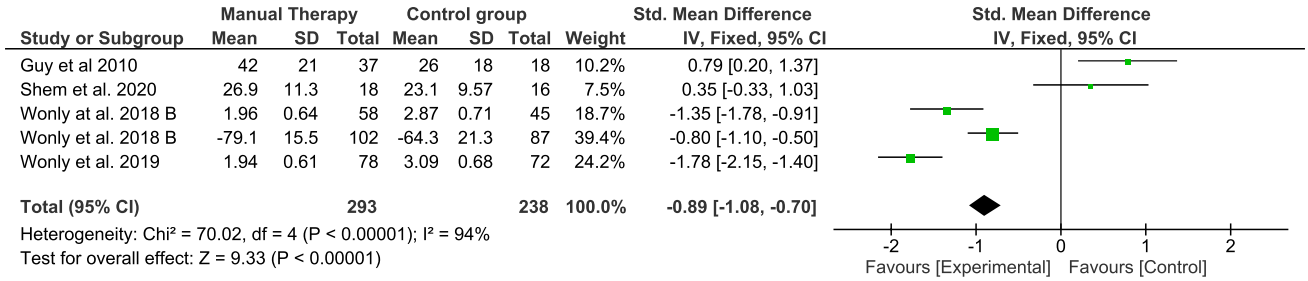

Fig. 4 Forest plot of comparison. Manual therapy vs control group. Outcome: functional status scale (BCTS-Q)

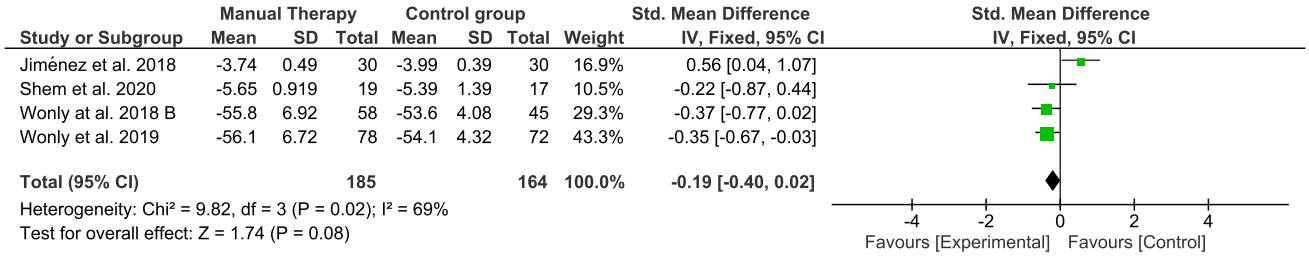

Fig. 5 Forest plot of comparison. Manual therapy vs control group. Outcome: nerve motor conduction

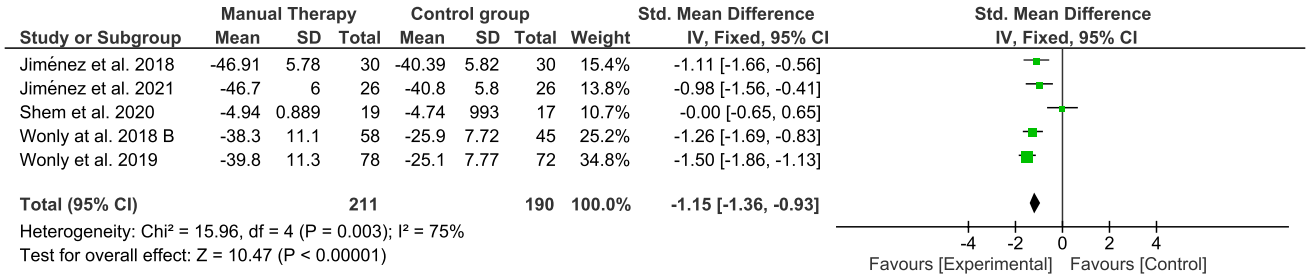

Fig. 6 Forest plot of comparison: manual therapy vs control group. Outcome: nerve sensory conduction

Five funnel plots were performed, one for each outcome assessed in this meta- analysis, where changes between manual therapies over the control group were assessed (Figs. 2, 3, 4, 5, 6). In most of them, there seems to appear a good symmetry in the funnel plots; thus, we consider that there is no publication bias. However, for the pain assessment, there seems to be a clear symmetry favoring the studies reporting improvement in this outcome.

Discussion

The results of this systematic review suggest that conservative treatment based on manual therapy is effective for reducing pain intensity and improve function and nerve conduction studies compared to control or sham in patients CTS.

To our knowledge, this is the first meta-analysis that summarizes manual therapy interventions in patients with CTS. Several systematic reviews have been published including different conservative treatments such as electrotherapy, splinting, therapeutic exercise, or drugs [29–31].

In view of the results, our meta-analysis shows statistical differences between diacutaneous fibrolysis technique to sham or control [15, 26]; glide and tension neurodynamic techniques to sham on symptom function and nerve conduction studies [14, 25, 27]. On the other hand, there were no statistical differences between bone mobilization and neurodynamic techniques; also, the self-myofascial stretching of carpal ligament did not show significant differences on symptoms or function [28].

The results of this meta-analysis are consistent with the previous systematic reviews that showed positive effects after manual therapy treatment on symptoms and function in patients with CTS [21, 29, 31–33]. In these reviews, the

intervention included all conservative treatments, whereas in this meta-analysis, the effect of manual therapy interventions in isolation was analyzed.

Diacutaneous fibrolysis effects were analyzed in two studies included in that meta-analysis. They found statistical differences on pain intensity, function, nerve conduction studies, and mechanosensitivity [15, 26]. Several authors have hypothesized the use of soft tissue mobilization around the median nerve to decrease the compression and improve symptoms in patients with CTS [18, 34–37]. Although it has not been studied in depth yet, it seems that the mechanism of diacutaneous fibrolysis could impact on tissue adhesion and increase the connective tissue mobility [38–40]. Thus, as previous authors have suggested, the instrumental soft tissue mobilization of the forearm and wrist could improve the median nerve gliding in the carpal tunnel in patients with CTS [26, 35, 41].

Shem et al. (2020) [28] investigated a self-stretching protocol of carpal tunnel and did not find any difference in any variable. The intervention group's positive effects did not achieve statistical significance differences compared to the sham group [28]. The self-stretching technique may not be as effective as the intervention applied by the therapist, which may explain the lack of statistically significant results.

Neurodynamic mobilization techniques were applied in three studies included in this meta-analysis. In two of them, the technique was performed by the therapist, based on glide and tension mobilizations. Compared to sham or control groups, more significant results on symptoms, function, and nerve conduction studies were found. Neurodynamic techniques have been proposed to improve the neurophysiological functions of the median nerve and reduce symptoms in patients with CTS [27, 42]. As the median nerve has a lack of longitudinal and transverse excursion, neural mobilizations could restore the normal movement [43]. Our findings are in line with previous authors. Nevertheless, unlike us, they included combined techniques in their treatment protocols, whereas in this meta-analysis, the effects of neurodynamic technique in isolation were analyzed [30, 44, 45].

By contrast, Tal-akabi et al. (2007) did not found differences between neurodynamic and bone mobilization with flexor retinaculum stretch [14]. In this study, the treatment of the interface aimed with musculoskeletal mobilization may positively effect on the neural compression status. In this sense, the comparison between both techniques could not be different in the assessment after one treatment session.

The results observed in this meta-analysis show that the passive intervention based on manual therapy significantly improved pain intensity decrease. This results are in accordance to previous studies that recommend the using conservative treatment to manage symptoms in patients with CTS [4, 12, 29]. A comprehensive model previously proposed could explain the positive effects on pain intensity applying manual therapy, which means that a mechanical force from manual therapy initiates a cascade of neurophysiological responses from the peripheral and central nervous system responsible for the clinical outcomes [19].

BCTS questionnaire is a valid tool to assess symptom severity and function in patients with CTS [46]. All the interventions improved this variable except to self-treatment group. Also, there were no differences between bone carpal mobilizations and neurodynamic techniques.

As previous studies have determined the statistical difference obtained after the interventions included in this meta-analysis, they achieved minimal clinically important difference [47].

Nerve conduction studies are the gold standard for CTS diagnosis to assess the sensory conduction velocity and distal motor latency. The correlation between this variable and symptoms is still not clear [42, 48]. However, nerve conduction studies have potentially great value not only in selecting patients for a specific treatment but also in the objective assessment of treatment efficacy in CTS, especially when they significantly correlate with clinical outcome measures. Neurodynamic mobilizations and diacutaneous fibrolysis techniques obtained statistical significance in nerve conduction studies after treatment. No previous studies providing data on the minimum detectable difference in the values obtained in the neurophysiological parameters were found. The results of this meta-analysis are in accordance to previous studies that applied conservative treatment achieved improvements on nerve conduction studies [49] but differ from others that no showed significant differences [50, 51]. Again, it is important to highlight that the interventions were applied in isolation compared to previous studies that combined many treatments.

Methodological quality analysis showed a high overall quality supporting the results observed in this systematic review. The most shared bias in the studies included was the lack of blinding of the therapist who administered the therapy and the analysis by intention to treat. These aspects are usual in previous reviews of clinical trial involving manual therapy techniques.

There are some limitations of this systematic review and meta-analysis. Therefore, the obtained results should be interpreted with caution. First, as reflected in the statistic heterogeneity study of the meta-analysis, the included studies have shown from moderate to high heterogeneity. Despite the clinical use of manual therapy techniques, the lack of randomized clinical trials leads to pull different techniques under the same concept and thus to increase methodological heterogeneity. Because of technique variability, the number of sessions and the total duration of treatment differ between the studies. Moreover, the dependent variables and the protocol assessment were heterogeneous.

Future research applying manual therapy on patients with CTS is needed in order to support its effectiveness. Moreover, a follow-up may be interesting to analyze if the improvements are maintained in the long-term.

Conclusion

This study highlights the effectiveness of manual therapy techniques based on soft tissue and neurodynamic mobilizations, in isolation, on pain, physical function, and nerve conduction studies in patients with CTS.

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Author contribution All authors made substantial contributions to the conception or design of the work: or the acquisition, analyses, or interpretation of data; drafted the work or revised it critically for important intellectual content; approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations

This study design and protocol were performed in accordance with the PRISMA Statement. The protocol was registered previously on PROSPERO CRD42020167559.
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Ethical approval and consent to participate Not applicable.

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Competing interest The authors declare no competing interests.

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CLINICAL RESEARCH ARTICLE

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Ultrasound therapy adds no benefit to splinting in carpal tunnel syndrome

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Abstract

Introduction: Therapeutic ultrasound has been suggested as a treatment for carpal tunnel syndrome (CTS), but existing trial evidence is of poor quality and inconclusive.

Methods: We conducted a randomized, controlled trial of therapeutic ultrasound in mild to moderate CTS. Forty patients were treated with wrist splints plus either real or sham therapeutic ultrasound and followed for 1 year posttreatment. The primary outcome was change in symptom severity scale score. Secondary outcomes were functional status scale score, nerve conduction studies, and ultrasound imaging of the median nerve.

Results: Both groups showed significant clinical and neurophysiological improvement at 6 and 12 months compared with baseline. There were no significant differences between groups at any time. In a multivariate analysis, the only independently significant predictors of the primary outcome were pretreatment symptom severity and additional treatments during follow-up.

Discussion: We found no clinically significant benefit from ultrasound treatment for CTS.

KEYWORDS

Boston Carpal Tunnel Questionnaire, carpal tunnel syndrome, placebo-controlled trial, randomized, ultrasound imaging, ultrasound therapy

1 | INTRODUCTION

Many treatments have been proposed for treating carpal tunnel syndrome (CTS), but only three are supported by high quality evidence—splinting, corticosteroids, and surgery. Splinting alone probably has a success rate of 34%.[1] Corticosteroid injection is highly effective but effects are often short-lived.[2] It is, however, very safe with less than 0.1% serious complications.[3] Surgery is generally considered the definitive treatment, but it results in a small but significant incidence of permanent morbidity from complications.[4] Because all three alternatives have failings, there are valid grounds for exploring alternative treatments.

Abbreviations: BCTQ, Boston Carpal Tunnel Questionnaire; CSA, cross-sectional area of median nerve on ultrasound imaging; CTS, carpal tunnel syndrome; FSS, functional status scale; MCID, minimal clinically significant difference; NCS, nerve conduction study; NCS-grade, Canterbury neurophysiological severity grade for CTS; SSS, symptom severity scale.

Therapeutic ultrasound has been used for pain relief in many musculoskeletal diseases and may have the potential to induce biophysical effects within tissue,[5] although the physical basis of this has been questioned, and there is little evidence of therapeutic benefit other than that which might be expected from the mild heating effect of ultrasound.[6,7] Several studies have explored its use in CTS, in comparison either to placebo or to other treatments.[8-12] A Cochrane review concluded that there is only poor quality evidence from very limited data to suggest that therapeutic ultrasound may be more effective than placebo for either short- or long-term symptom improvement in CTS and called explicitly for further studies, prompting us to plan this study.[13] A more recent systematic review found moderate evidence of benefit from ultrasound in the midterm, by which the authors appear to have meant 6 months follow-up.[14] The objective of this study was, therefore, to determine whether wrist splinting plus

therapeutic ultrasound is more effective than wrist splinting plus sham ultrasound therapy (placebo) in mild to moderate CTS.

2 | MATERIALS AND METHODS

This was a randomized, double blind, single-center, trial conducted at East Kent Hospitals University NHS Foundation Trust, Kent and Canterbury Hospital, United Kingdom. This study was conducted in compliance with the protocol of the *Guideline for Good Clinical Practice*, Research Governance Framework for Health and Social Care, and United Kingdom regulatory requirements. Approval was obtained from National Research Ethics Service committee South East Coast-Kent (reference No. 11/LO/1576; Nov 2011), and Research and Development approval was obtained from EKHUFT R&D (reference No. 2011/NEURO/04). The trial was registered with Clinicaltrials.gov (trial identification No. NCT01590745). Recruitment began in June 2012 and was completed in November 2016 after the intended sample size of 40 was reached. Follow-up was completed in January 2018.

Participants were recruited from patients referred for suspected CTS to a dedicated CTS clinic by either primary physicians or hospital specialists. Men and women aged 18 to 90 years with symptoms consistent with CTS confirmed by nerve conduction abnormalities of the Canterbury neurophysiological severity grade for CTS grades (NCS-grade) 1–3[15] were eligible for the study. This excluded patients with absent median sensory potentials and those with median motor latencies to abductor pollicis brevis >6.5 ms. Participants were also excluded if they had any previous treatment for CTS other than splinting and use of over the counter analgesics or current diagnoses of polyneuropathy, diabetes mellitus, rheumatoid disease, acute trauma, human immunodeficiency virus infection, pregnancy, or lactation. Participants with other serious medical or psychiatric illness that, in the opinion of the investigator, would compromise the study and those unable to complete the assessments because of language barriers were also excluded. In participants with bilateral CTS, only one hand, the worst affected or the dominant hand in symmetrical cases, was used for the study. If CTS in the hand not being used in the study was severe enough to require treatment this was treated concurrently with splints and/or corticosteroid injection. All participants gave fully informed written consent.

The primary outcome measure was the Boston Carpal Tunnel Questionnaire (BCTQ) symptom severity subscale (SSS) at 12-month follow-up.[16] Secondary outcome measures consisted of nerve conduction studies (NCS) carried out according to American Association of Neuromuscular & Electrodiagnostic Medicine standards, ultrasound imaging of the median nerves with measurement of cross-sectional area (CSA), the functional status subscale (FSS) of the BCTQ, the participants overall assessment of treatment outcome, and the requirement for additional treatment for CTS after the 7-week intervention period. All assessments were made at recruitment, at completion of treatment (7 weeks), and at 6 and 12 months postrecruitment. All ultrasound imaging was performed by the senior author (J.B) using a Sonosite ultrasound scanner equipped with a 7 to 14 MHZ linear transducer. Cross-sectional area (CSA) measurements were made of the largest point of the median nerve immediately proximal to the wrist by using the outline tracing method on images magnified by a factor of 2 in the inbuilt scanner software.

Randomization was by computer-generated random sequence. Sealed opaque envelopes containing the group allocation were opened only at commencement of treatment. Unblinding was carried out only after trial completion and data analysis.

In the absence of any evidence favouring a particular choice of frequency or intensity for ultrasound treatment of CTS,[14] we chose to replicate the treatment protocol used in a previous, good quality trial in which significant benefit in the active treatment group was reported.[8] The active treatment group received pulsed mode ultrasound treatment for 15 minutes per session for 20 sessions at 1 MHZ/1.0 W/cm^2, 5 times weekly for the first 2 weeks then twice weekly for the next 5 weeks with commercially available ultrasound equipment (Therasonic 460 Primo; EMS Physio). The sham treatment group (placebo) received unpowered ultrasound (setup at 0.0 MHZ/0.0 W/cm^2), achieved by delivering treatment in the same manner with the machine switched off. The ultrasound treatment was carried out by mild stroking in a figure-8 pattern with a circular probe held perpendicular to the wrist. To conceal from the patient and treating investigator whether the ultrasound probe was active, several precautions had to be taken. Lights on the ultrasound probe indicating activity were concealed with masking tape. The coupling gel used was warmed to 33°C to conceal any heating effect from the active treatment. Background music was played to obscure the faint sounds made by the active machine, and the main body of the machine and power switches were screened from the patient and treating investigator and operated by a third person who opened the treatment allocation envelopes at the first treatment session and remained the only individual involved in the study who knew the group allocation. This individual played no part in the study beyond opening the treatment allocation envelope and setting the ultrasound machine to either on or off and had no contact with the trial participants.

All participants were given wrist splint(s) to be worn at night until symptoms resolved.

Participants were asked not to use any interventions for CTS during the 7-week treatment period apart from splints; after the trial treatment period, if they had significant continuing symptoms of CTS, they proceeded to conventional treatment by corticosteroid injection and/or surgery, as required.

The study participants, ultrasound therapist, and investigators carrying out the NCS and ultrasound examinations were blinded to treatment allocation for the entire trial period. At completion of the 7-week treatment period and at the end of participation in the study, participants were asked to guess whether they had been in the active or sham treatment groups as a check on the success of blinding.

A decrease of approximately 1 point is considered the minimal clinically significant difference (MCID) for the SSS.[17-19] Detection of a difference between the active and placebo groups of this magnitude at a confidence level of 95% and power 0.95 with a standard

deviation for the SSS score obtained from our patients of 0.84 units was calculated to require 20 patients per group. This group size also facilitated comparison with the study we were replicating.[8]

Statistical analysis was carried out in Statistica 13. Baseline demographic characteristics and outcome measures were compared by using *t* tests for normally distributed variables, Mann–Whitney U tests for nonnormally distributed variables, and Fisher's exact test for categorical variables. The significance level was set at $P < .05$. We also used a multivariate regression model with improvement from baseline to final SSS score as the dependent variable and treatment group as one of the independent variables in an attempt to determine whether group allocation was an independently significant predictor of outcome.

3 | RESULTS

There were no significant demographic or outcome variable imbalances between active treatment and sham treatment groups at baseline (Table 1). There were no treatment protocol violations, and all participants completed treatment as planned. All participants completed 6 months of follow-up, but one patient in each group failed to attend for the 12-month follow-up and could not be contacted subsequently. Patient flow through the study is shown in the consort diagram (Figure 1).

Both groups showed significant improvement in the primary outcome at 7-week, 6-month, and 12-month follow-ups (Table 2) as well as improvement in both nerve conduction results and ultrasound CSA measurements (Table S1), but there were no significant differences between groups at any time point. Participants performed no better than chance at guessing whether they had been in the active or placebo groups.

During the 1-year study follow-up, seven of 20 (35%) participants in the sham treatment group and eight of 20 (40%) participants in the active treatment group required corticosteroid injection in the study hand (Fisher's exact test $P > .99$). One patient in the sham treatment group and two patients in the active treatment group had a second injection, and one patient in the sham treatment group had a third injection. One patient in the sham treatment group required surgical decompression. This use of additional treatment for CTS in the study hand was not significantly different between groups (Fisher's exact test $P > .99$).

In the multivariate analysis (Table 3), the only independently significant predictors of improvement in SSS score at 12-month follow-up were the number of corticosteroid injections given after the trial treatment, surgery carried out during follow-up, and the baseline SSS score. Treatment group was not a significant predictor.

4 | DISCUSSION

This randomized, controlled trial demonstrated no clinically significant benefit from the addition of ultrasound treatment to splinting for CTS compared with sham ultrasound treatment plus splinting either in the short term at the end of active treatment at 7 weeks or at 1-year posttreatment. As is common in treatment trials for mild to moderate CTS, both the active treatment and placebo groups improved with respect to baseline in both subjective (SSS) and objective (NCS-grade and ultrasound CSA) measures. This finding probably results from a combination of factors including regression to the mean in a naturally variable condition, the effect of splinting in both groups, placebo effects, and nonspecific benefits from being involved in a treatment trial. It is notable, however, that the improvement in SSS score achieved during this study was less than the suggested MCID in this measure. It is not clear whether this is because the improvement in our patients was truly not clinically important or because previous estimates of the MCID are too large. Most of our patients chose not to pursue additional treatment during follow-up, which suggested that

TABLE 1 Baseline assessments before treatment

Baseline variables	Sham therapy	Active therapy
Age, mean (SD), y	58.27 (10.84)	53.46 (10.71)
Sex, n		
Men	3	6
Women	17	14
Study hand side, n		
Right	16	14
Left	4	6
NCS-grade study hand, n		
1	8	9
2	5	3
3	7	8
Average (SD)	1.95 (0.88)	1.95 (0.94)
NCS-grade other hand, n		
0	8	6
1	8	7
2	1	6
3	3	1
Average (SD)	0.95 (1.05)	1.1 (0.91)
SSS, study hand, mean (SD)	2.54 (0.80)	2.55 (0.7)
FSS, study hand, mean (SD)	1.91 (0.78)	1.97 (0.96)
SSS, other hand, mean (SD)	1.97 (0.66)	1.98 (0.88)
FSS, other hand, mean (SD)	1.52 (0.76)	1.64 (0.81)
CSA, study hand, mean (SD), mm^2	14.4 (5.36)	13.3 (3.83)
CSA, other hand, mean (SD), mm^2	12.4 (3.85)	11.7 (3.51)
DML, study hand, mean (SD), ms	4.37 (0.82)	4.29 (0.58)
DML, other hand, mean (SD), ms	3.67 (0.64)	3.72 (0.6)
SCV, study hand, mean (SD), m/s	39.4 (6.41)	40.17 (4.57)
SCV, other hand, mean (SD), m/s	45.5 (8.14)	44.6 (7.12)

Abbreviations: CSA, cross-sectional area on ultrasound imaging; DML, distal motor latency to abductor pollicis brevis; NCS-grade, Canterbury neurophysiological severity grade for carpal tunnel syndrome; SSS, symptom severity scale score; FSS, functional status scale score; SCV, sensory conduction velocity (median nerve).

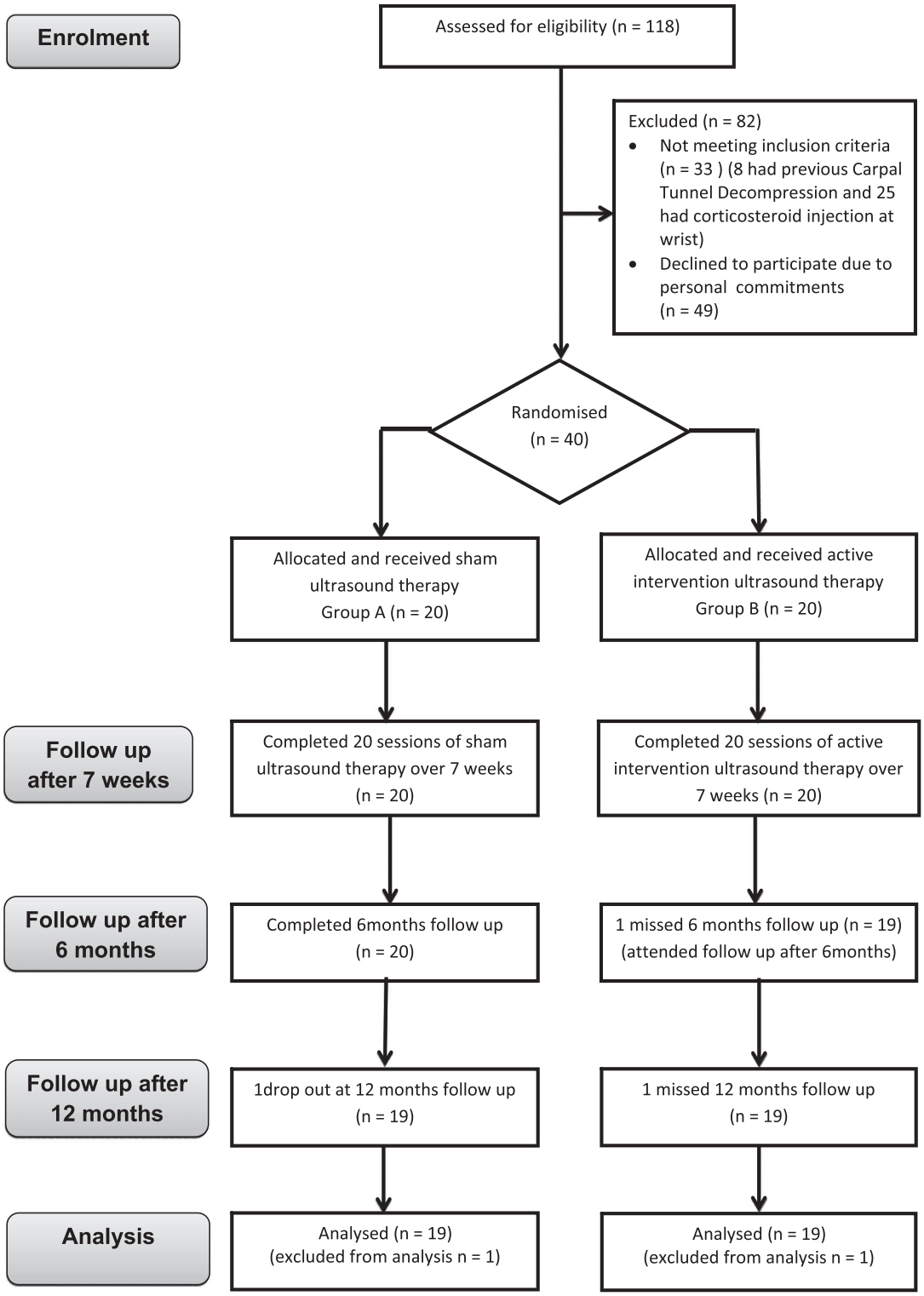

FIGURE 1 Consort diagram illustrating patient flow through the study

they felt that their symptoms had improved meaningfully. The mean change in SSS score after 1 year in these patients was 0.76 units, which perhaps indicated that prior estimates of the MCID are indeed too large.

Our findings differ from those of Ebenbichler and colleagues,[8] whose treatment regime we attempted to replicate. The Ebenbichler et al[8] study had several methodological problems. The hand rather than the patient was used as the unit of analysis, with two hands from each participant being included in the study, the success of blinding was not checked, and there were significant losses to follow-up (11/45 patients at 7 weeks and 15/45 patients at 6 months). They also used a nonstandard primary subjective outcome measure, visual

TABLE 2 Improvement in symptom severity score at each follow-up assessment compared with baseline

Follow-up interval	n	Mean (SD)	95% Confidence limits	P
	Sham therapy group			
7 weeks	20	0.42 (0.74)	0.08–0.77	.019
6 months	20	0.77 (0.73)	0.43–1.11	<.001
2 months	19	0.83 (0.93)	0.38–1.28	.001
	Active therapy group			
7 weeks	20	0.55 (0.73)	0.21–0.89	.003
6 months	20	0.76 (0.97)	0.30–1.21	.002
12 months	19	0.69 (0.90)	025–1.12	.004
	Between group comparisons			
		Difference in means	**95% confidence limits**	
7 weeks	20	0.13	–0.34-0.59	.59
6 months	20	0.01	–0.56-0.54	.97
12 months	19	0.12	–0.8-0.55	.71

TABLE 3 Multivariate analysis of predictors of change in symptom severity score from baseline at 12-month follow-up

			Confidence limits		
Predictor variables	**Parameter estimate**	**Standard error**	**–95%**	**95%**	**P**
Intercept	0.00	0.79	–1.66	1.64	.99
Baseline symptom severity score	0.74	0.16	0.39	1.08	.00
Age, per year	0.00	0.01	0.02	0.02	.87
No. of injections during follow-up	–0.38	0.14	–0.08	–0.08	.02
Sex	0.10	0.16	0.43	0.43	.50
Sham or active treatment group	0.03	0.12	0.27	0.28	.77
Operation during follow-up	–0.69	0.32	–0.03	–0.03	.04
Whole model performance	Multiple	Multiple	Adjusted		
	R	R^2	R^2		
	0.79	0.63	0.52		

analog scales for "whatever symptom the participant felt was the worst," which could not be replicated reliably. The positive findings in the earlier article may have been a result of these methodological biases.

Strengths of our study include demonstrably successful blinding of participants, almost complete follow-up for a prolonged period, and a wide range of outcome measures. Although in ordinary clinical practice ultrasound treatment can be self-administered by the patient at home, to achieve blinding for this study, the treatment had to be delivered in the clinic, and it proved difficult to recruit patients to a study that involved many appointments at the hospital during a 7-week period for treatment, perhaps biasing the study population toward those with ample leisure time.

We will be adding this study to the existing Cochrane meta-analysis of trials of ultrasound treatment for CTS, but our results provide evidence that this intervention is not a promising treatment for CTS.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest to disclose.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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