Neural Recovery After Carpal Tunnel Release: A Systematic Review with Meta-Analysis

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Abstract

Objective

The primary aim was to quantify changes in structural and functional nerve parameters following carpal tunnel release (CTR). The secondary aims were to describe recovery trajectories and describe the regenerative capacity of the median nerve.

Design

Prognosis systematic review with meta-analysis

Literature search and selection criteria

Six databases were searched from inception to June 2024 for studies reporting at least one of the following outcomes: electrodiagnostic measures, quantitative sensory testing, grip/pinch strength, two-point discrimination, Semmes-Weinstein monofilament, intraepidermal nerve fiber density (IENFD), autonomic measures, brain function/structure, or Boston carpal tunnel questionnaire.

Data synthesis

Outcomes were categorized by time post-surgery: <2, 2–4, 5–7, 8–12, and >12 months. Randomized and observational studies were included, with quality assessed using the RoB 2 tool and the Newcastle–Ottawa Scale, respectively.

Results

A total of 199 studies comprising 15,636 patients and 578 healthy controls were included. We observed significant, time-dependent improvement in most outcomes. Grip and pinch strength did not show marked recovery until 5–7 months postoperatively. Compared to healthy controls, patients had persistent deficits in several electrodiagnostic measures even one year after surgery. Impairments in warm,

vibration, and mechanical detection thresholds persisted up to 6 months postoperatively.

Conclusion

CTR led to gradual improvement in median nerve function and structure. Key measures —including electrodiagnostics, detection thresholds, and IENFD—often remained below normal levels after surgery.

Keywords: Carpal tunnel syndrome, Neural recovery, Electrodiagnosis, Quantitative sensory testing, Intraepidermal nerve fibre density, Grip strength

Introduction

Carpal tunnel syndrome (CTS) is a focal compression of the median nerve at the carpal tunnel, resulting in pain, paresthesia, and potential weakness of the affected hand [157]. The pathophysiology involved in CTS includes changes to peripheral and central nervous system function and structure, as evidenced by alterations to median nerve conduction studies [6], somatosensory function upon quantitative sensory testing (QST)[188], cutaneous innervation on skin biopsies [21], or brain imaging [155].

Mild to moderate CTS often responds well to non-surgical management strategies, whereas severe cases typically require surgical intervention [157,225]. One in 3 patients who have a carpal tunnel release report persistent numbness and pain [24,65,100,233]. Of those with persistent symptoms, 1 in 20 may need revision surgery. Male sex, bilateral carpal tunnel surgery, rheumatoid arthritis, endoscopic release, diabetes, cervical problems, psychiatric conditions, and smoking are risk factors for revision surgery [222,223].

While there are some summary data on the development of symptoms and disability after surgery [24,132], no systematic reviews have summarized the evidence for changes in nerve structure or function following carpal tunnel surgery. This knowledge is crucial for providing realistic information about expected surgical outcomes to patients, and understanding postoperative nerve regeneration capacity.

We describe the extent of change in measures representing nerve structure and function in patients undergoing carpal tunnel release (pre-surgical versus post-surgical outcomes, and post-surgical versus healthy control). We included measures of sensory and motor nerve conduction, autonomic parameters, skin biopsy parameters, somatosensory function, grip and pinch strength, and functional brain connectivity. We also examined changes in symptom severity and function. The primary aim was to quantify changes in structural and functional nerve parameters following carpal tunnel release. The secondary aims were to describe recovery trajectories and describe the regenerative capacity of the median nerve.

Methods

Our review protocol was previously registered (PROSPERO: CRD42023454973) and our reporting followed PRISMA guidelines [158].

Eligibility criteria

Randomized controlled trials (RCTs) and observational studies were eligible if the following criteria were met: 1) Studies involved adults (age ≥ 18 years) with any type of CTS release surgery; 2) Studies investigated any of the following outcomes: nerve conduction studies, QST, intraepidermal nerve fiber density (IENFD) on skin biopsies, hand motor function, two point discrimination (2PD), Semmes-Weinstein monofilament

test (SWM), sympathetic skin response, thermography, brain structure and function, symptom severity and function; and 3) Studies published in English. The exclusion criteria were studies that: 1) included patients under 18 years; 2) included revision surgery; 3) included patients with CTS and concomitant neuropathies (e.g., diabetic neuropathy, mononeuritis multiplex, radial or ulnar neuropathies) or systemic illness. In addition to RCTs we also included observational studies, as we were not interested in the specific effects of surgery, but rather in the biological effects of postoperative nerve regeneration in general (which can include unspecific effects such as natural history.

Search strategy and information sources

We searched PubMed, Scopus, Web of Science, ProQuest, SAGE, and Cochrane Library databases from inception to June 2024 (**Appendix 1**). A manual search of reference lists of included studies was also performed.

Selection process

After removing duplicates using EndNote 9.0, titles and abstracts were screened by two independent reiewers (AM and AS). Full texts of potentially eligible studies were then checked for final inclusion by two independent reviewers (MS and KH). Disagreement was resolved by a third reviewer (MS).

Data extraction

From each included study, two reviewers (FK and SY) independently extracted the following data: number of participants, age, gender, time interval for follow-up, investigated outcomes and methods of assessment and results. Summary data (e.g.,

mean and standard deviations (SD)) were extracted at all available time points by two independent reviewers (FK and SY) for QST battery, nerve conduction studies (median, ulnar, and radial), hand motor function, IENFD, brain function and structure, 2PD, SWM, autonomic measures, and the Boston carpal tunnel questionnaire (BCTQ-symptom severity, and BCTQ-function). Plot digitizer [88] and snipping tool programs were used to extract data from graphs when summary data were not available. Alternative summary statistics were transformed to means and SD using recommended calculations [88,218]. Agreement of extracted summary data was checked by a third reviewer (MS). If important information could not be obtained from the paper, the primary author was contacted once to request the data.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included observational studies [190]. For randomized controlled trials, the ROB2 tool was used [192]. Two reviewers independently rated the quality of included studies (ME and FK). If there were disagreements, a third reviewer arbitrated (MS).

Analysis

As numerous electrophysiological parameters and clinical outcomes were expected at various intervals, time points were pooled to <2, 2-4, 5-7, 8-12, and >12 months. The selection of those timepoints was based on the commonly investigated time windows within the included studies.

If at least two studies reported the same outcome measures using similar assessment methodology, meta-analysis was performed. Two comparisons were

performed at all time points with available data: 1) pre- versus post-surgery and 2) post-surgery versus healthy controls. Statistical analyses were performed in Review Manager (RevMan, v5.4, Cochrane Collaboration, Oxford, UK). Group means, SD, and sample sizes were used to calculate standardized mean differences (SMD) and 95% confidence intervals (CI) using random effects models. The overall effect was categorized as very large (>2.0), large (1.21-2.0), moderate (0.61-1.2), small (0.2-0.6), or trivial (<0.2) [76]. When the same study provided data for open versus arthroscopic surgery, surgery of moderate versus severe CTS, or surgery of males versus females, we included each group separately in the meta-analyses. Statistical significance was determined at p-value < 0.05. Heterogeneity was analysed by using (I^2) and classified as: 0%-40%: '*might not be important*', 30%-60%: *moderate*, 50%-90%: *substantial* and 75%-100%: *considerable* [74]. To calculate the average age of all participants with CTS included in this study, we used the arithmetic mean.

Publication bias was assessed using Egger's regression test and visually represented with funnel plots. P-values of Egger's regression tests were considered significant if less than 0.1. In this case, the trim and fill method of Duvall and Tweedie was used if there were 10 or more studies, to impute theoretically missing studies [46]. The strength of evidence for each outcome measure at each time-point was determined according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[38]. The overall certainty of evidence was primarily determined by the highest-quality study designs (RCTs), with findings from observational studies used to complement and support the primary evidence base.

Results not included in the meta-analyses were described using narrative synthesis of measures of nerve function and structure. We used the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews: A Product from the ESRC Methods Programme (2006) to report our findings [161].

Results

The electronic database search returned 1947 records. After removing duplicates, checking against eligibility criteria, and searching bibliographies of relevant articles, 199 studies were retained, with 146 included in the meta-analysis **(Figure 1).**

Study characteristics

There were 155 observational studies [4,5,8,10,11,13,15–22,25,27,28,31,35–37,39,41,42,48,49,51–53,59–61,64,66,67,70–73,75,77,80–86,89–93,95–98,101–107,109,110,114,116,117,121,122,125,126,128–131,134–137,140–152,154–156,159,160,162–168,171–175,180,181,183,185,186,189,191,193–203,205–217,219–221,224,227–232,236,237,240] and 44 randomized controlled trials [3,7,9,12,23,26,29,30,32,33,43,44,47,50,54–57,62,68,78,79,87,94,108,111,118–120,124,133,138,139,169,176,179,182,184,204,226,234,235,238,239] **(Appendix 2)**. Studies included 15,636 patients and 578 controls. The mean age of participants with CTS was 54.2 years; 68% (n= 10594) were females. Endoscopic and open carpal tunnel releases were the most frequent surgeries. The type of surgery was not identified in 9 studies.

Quality assessment

Most of the observational studies (n=145) were of fair to good quality with a Newcastle Ottawa Scale score of at least 5 (**Table 1**). Forty-four trials were assessed: 30 were at high risk of bias, 5 had some concerns, and 9 were at low risk of bias (**Figure 2**). The details of the 5 bias domains are depicted in **Figure 3**.

Outcome measures

Measures of nerve function and structure included electrophysiological parameters of median, ulnar, and radial nerves, QST (cold, warm, vibration, and mechanical detection thresholds (CDT, WDT, VDT, MDT), cold, heat, mechanical, and pressure pain thresholds (CPT, HPT, MPT, PPT), mechanical pain sensitivity (MPS), wind-up ratio (WUP), thermal sensory limen (TSL)), IENFD, 2PD, SWM, hand motor function, autonomic measures including sympathetic skin response and infrared hand thermography, brain function and structure, and BCTQ symptom and function measures. The summary of results for each variable at each time-point is presented in **Table 2**, with additional details on the effect size and strength of evidence. Descriptive results are in **Appendix 3** and funnel plots are in **Appendix 4**.

A- Pre-post comparisons

1- Median nerve conduction studies

1.1. Distal motor latencies (DML)

The overall effect of surgical release on DML was large improvements compared to pre-operative level (SMD: 1.34, CI [1.24, 1.45], p< 0.00001, I^2= 85, 65 studies, low certainty evidence, Figure 1.1).

Subgroup analyses at different timepoints demonstrated significant improvements of DML: <2 months after surgery (SMD: 1.00, CI [0.72, 1.28], p <0.00001, moderate certainty evidence), with significant publication bias (p < 0.001). The effect size after adjusting for the missed studies was (SMD: 1.4, CI [1.1, 1.7], p <0.00001). At 2-4 months (SMD: 1.16, CI [1.03, 1.30], p <0.00001, low certainty evidence), with

significant publication bias (p < 0.001). The effect size after adjusting for the missed studies was SMD: 1.0, CI [0.9, 1.1], p <0.00001. At 5-7 months (SMD: 1.38, CI [1.19, 1.56], p <0.00001, moderate certainty evidence). At 8-12 months (SMD: 1.72, CI [1.44, 2.00], p <0.00001, low certainty evidence). At >12 months (SMD: 2.08, CI [1.78, 2.39], p<0.00001, moderate certainty evidence).

1.2 Motor conduction velocities (MCV)

The overall effect of CT release on MCV was large improvements compared to pre-surgery (SMD: -1.48, CI [-2.1, -0.86], p< 0.00001, I2= 94%, 10 studies, low certainty evidence) (Figure 1.2). All studies measured MCV from wrist-median nerve segment.

There was low certainty evidence of a moderate improvement at 2-4 months (SMD: -0.98, CI [-1.58, -0.38], p = 0.001), large changes at 5-7 months (SMD: -1.42 [-2.53, -0.32, p = 0.01], low certainty evidence), and very large changes at 8-12 months (SMD: -4.43 [-6.25, -2.61], p <0.00001, low certainty evidence).

1.3 Compound Motor Action Potential amplitudes (CMAP)

The overall effect of CT release on CMAP was small improvements compared to pre-operative levels (SMD: -0.40, CI [-0.53, -0.26], p< 0.00001, I^2= 84%, 34 studies, very low certainty evidence) (Figure 1.3).

At <2 months post-surgery, there was no change in CMAP (SMD 0.09, CI [-0.04, 0.21], p= 0.43, low certainty evidence), low certainty evidence of small improvements at 2-4 months (SMD: -0.37, CI [-0.62, -0.11], p = 0.005) and at 5-7 months (SMD: -0.41, CI

[-0.55, -0.27], p<0.00001, very low certainty evidence) with moderate improvements at 8-12 months (SMD: -0.72, CI [-1.17, -0.27], p = 0.002, low certainty evidence).

1.4 Sensory conduction velocities (SCV)

The overall effect of CT release on SCV was large improvements compared to pre-operative levels (SMD: -1.51, CI [-1.66, -1.36], p< 0.00001, I^2= 89%, 45 studies, low certainty evidence) (Figure 1.4).

There were moderate improvements in SCV at <2 months (SMD= -1.12, CI [-1.53, -0.72], p <0.00001, low certainty evidence) and 2-4 months (SMD: -1.16, CI [-1.37, -0.96], p <0.00001, low certainty evidence), large improvements at 5-7 months (SMD: -1.67, CI [-1.92, -1.41], p <0.00001, low certainty evidence) and 8-12 months (SMD: -1.78, CI [-2.14, -1.43], p <0.00001, low certainty evidence), and very large improvements at >12 months (SMD: -2.65, CI [-3.53, -1.77], p <0.00001, low certainty evidence).

1.5 Sensory nerve action potential (SNAP)

The overall effect of CT release on SNAP was moderate improvements compared to pre-operative levels (SMD: -0.77, CI [-0.96, -0.58], p< 0.00001, I^2= 88, 26 studies, moderate certainty evidence) (Figure 1.5).

Subgroup analysis revealed evidence for improvement in SNAP at <2 months (SMD: -0.27, CI [-0.48, -0.07], p = 0.01, low certainty evidence), low certainty evidence for moderate improvements at 2-4 months (SMD: -0.73 [-1.06, -0.39], p < 0.0001) and 5-7 months (SMD: -0.61, CI [-0.85, -0.37], p<0.00001, low certainty evidence), with large

improvements at 8-12 months (SMD: -1.44 [-2.01, -0.86], p <0.00001, moderate certainty evidence) .

2- Quantitative sensory testing (QST)

2.1 Cold Detection Threshold (CDT)

The overall effect of CT release on CDT was small improvements compared to pre-operative levels (SMD: -0.41, CI [-0.55, -0.27], p< 0.00001, I^2= 0%, 7 studies, low certainty evidence) (Figure 2.1).

Subgroup analysis confirmed small improvements in CDT at <2 months (SMD: -0.52, CI [-1.00, -0.04], p = 0.03, low certainty evidence), 2-4 months (SMD: -0.36 [-0.57, -0.15], p = 0.0008, low certainty evidence), and 5-7 months (SMD: -0.44 [-0.73, -0.15], p = 0.003, low certainty evidence), with no significant change at 8-12 months (SMD: -0.40, CI [-0.80, 0.00], p= 0.05, low certainty evidence).

2.2 Warm detection threshold (WDT)

The overall effect of CT release on WDT was small improvements compared to pre-operative levels (SMD: 0.28, CI [0.09, 0.47], p< 0.004, I^2= 42%, 6 studies, low certainty evidence) (Figure 2.2).

There was evidence of a small improvement in WDT at <2 months (SMD: 0.40, CI [0.01, 0.80], p=0.04, low certainty evidence), 2-4 months (SMD: 0.26, CI [0.05, 0.47], p = 0.01, low certainty evidence), and no significant change at 5-7 months (SMD: 0.08, CI [-0.16, 0.33], p =0.52, very low certainty evidence) and at 8-12 months (SMD: 0.73, CI [-0.39, 1.85], p = 0.20, very low certainty evidence).

2.3 Thermal sensory limen (TSL)

There was evidence of a small improvement in TSL at 5-7 months (SMD: 0.35, CI [0.11, 0.60], p = 0.01, low certainty evidence) (Figure 2.3).

2.4 Cold pain threshold (CPT)

The overall effect of CT release on CPT was small but non-significant improvements in hyperalgesia compared to pre-operative levels (SMD: -0.22, CI [-0.43, -0.00], p< 0.05, I^2= 49%, 5 studies, low certainty evidence) (Figure 2.4).

There was evidence of a no change in CPT at 2-4 months (SMD: -0.21, CI [-0.52, 0.10], p = 0.18), and at 5-7 months (SMD-0.22, CI [-0.58, 0.14], p = 0.23, low certainty evidence).

2.5 Heat pain threshold (HPT)

The overall effect of CT release on HPT was no change compared to pre-operative level (SMD: 0.16, CI [-0.08, 0.39], p< 0.18, I^2= 67%, 6 studies, low certainty evidence) (Figure 2.5).

There was evidence of a small reduction in HPT at 2-4 months (SMD: 0.23, CI [0.01, 0.45], p = 0.04), with no change at 5-7 months (SMD: 0.20, CI [-0.19, 0.59], p = 0.32, very low certainty evidence), and at 8-12 months (SMD: -0.11, CI [-1.13, 0.91], p = 0.83, very low certainty evidence).

2.6 Pressure pain threshold (PPT)

The overall effect of CT release on PPT was small improvements compared to pre-operative levels (SMD: -0.03, CI [-0.14, 0.19], p< 0.75, I^2= 1%, 3 studies, low certainty evidence) (Figure 2.6).

There was evidence of no change in PPT at 2-4 months (SMD: -0.02, CI [-0.33, 0.29], p = 0.88, low certainty evidence), and at 5-7 months (SMD: 0.05, CI [-0.18, 0.28], p = 0.66, low certainty evidence).

2.7 Wind-up ratio (WUR)

The overall effect of CT release on WUR was no change compared to pre-operative levels (SMD: -0.02, CI [-0.21, 0.17], p< 0.81, I^2= 0%, 3 studies, low certainty evidence) (Figure 2.7).

There was evidence of no change in WUR at 2-4 months (SMD: 0.02, CI [-0.27, 0.31], p = 0.90, low certainty evidence), and 5-7 months (SMD: -0.05, CI [-0.30, 0.19], p = 0.68, low certainty evidence).

2.8 Vibration detection threshold (VDT)

The overall effect of CT release on VDT was small improvements compared to pre-operative levels (SMD: 0.23, CI [0.06, 0.41], p< 0.009, I^2= 29%, 6 studies, low certainty evidence) (Figure 2.8).

We found evidence of a small improvement in VDT at 2-4 months (SMD: 0.36, CI [0.15, 0.57], p = 0.0006), no change at 5-7 months (SMD: 0.31, CI [-0.07, 0.68], p = 0.11, very low certainty evidence), and small reduction at 8-12 months (SMD: 0.45, CI [0.09, 0.82], p = 0.02, low certainty evidence).

2.9 Mechanical pain threshold (MPT)

We found evidence of no change in MPT at 5-7 months (SMD: -0.01, CI [-0.40, 0.39], p = 0.98, very low certainty evidence) (Figure 2.9).

2.10 Mechanical pain sensitivity (MPS)

We found evidence of no change in MPS at 5-7 months (SMD: 0.08, CI [-0.23, 0.38], p = 0.61, very low certainty evidence) (Figure 2.10).

3- Bedside sensory assessment

3.1. Two-point discrimination (2PD)

The overall effect of CT release on 2PD was moderate improvements compared to pre-operative levels (SMD: 1.04, CI [0.87, 1.22], p< 0.00001, I^2= 92%, 27 studies, low certainty evidence) (Figure 3.1).

We found evidence of a small reduction in 2PD at <2 months (SMD: 0.36, CI [0.25, 0.48], p <0.00001, moderate certainty evidence), a moderate reduction at 2-4 months (SMD: 0.82, CI [0.62, 1.02], p <0.00001, low certainty evidence) and at 5-7 months (SMD: 1.14, CI [0.74, 1.54], p <0.00001, moderate certainty evidence), a large reduction at 8-12 months (SMD: 1.74, CI [1.14, 2.35], p <0.00001, low certainty evidence), and a very large reduction at >12 months (SMD: 2.34, CI [1.47, 3.21], p <0.0001, low certainty evidence).

3.2. Semmes Weinstein Filaments (SWM)

The overall effect of CT release on SWM was small improvements compared to pre-operative levels (SMD: 0.62, CI [0.50, 0.75], p < 0.00001, I^2= 90%, 21 studies, moderate certainty evidence) (Figure 3.2).

Subgroup analysis identified a small improvement in SWM at <2 months (SMD: 0.31, CI [0.17, 0.46], p < 0.0001, moderate certainty evidence), moderate improvements at 2-4 months (SMD: 0.69, CI [0.41, 0.98], p < 0.0001, moderate certainty evidence), small improvements at 5-7 months (SMD: 0.62, CI [0.42, 0.82], p < 0.00001, low

certainty evidence), and moderate improvements at 8-12 months (SMD: 1.12, CI [0.61, 1.63], p < 0.0001, low certainty evidence).

4- Grip Strength

The overall effect of CT release on grip strength was small improvements compared to pre-operative level (SMD: -0.24 [-0.42, -0.07], p= 0.006, I^2= 97%, 55 studies, low certainty evidence) (Figure 4.1).

There was evidence of a small decline in grip strength at less than 2 months (SMD: 0.65, CI [0.216, 1.02], p = 0.001, low certainty evidence), non-significant change at 2-4 months (SMD: -0.18, CI [-0.52, 0.15], p = 0.27, very low certainty evidence), small improvement at 5-7 months (SMD: -0.51, CI [-0.80, -0.22], p = 0.0005, low certainty evidence (, large improvement at 8-12 months (SMD: -1.06, CI [-1.41, -0.71], p <0.00001, very low certainty evidence) and very large improvements at >12 months (SMD: -1.27, CI [-2.24, -0.31], p = 0.01, low certainty evidence).

5- Pinch Strength

The overall effect of CT release on pinch strength was small improvements compared to pre-operative levels (SMD: -0.34, CI [-0.47, -0.21], p< 0.00001, I^2= 92%, 45 studies, very low certainty evidence) (Figure 5.1).

There was evidence of a small reduction in pinch strength at <2 months (SMD: 0.38, CI [0.22, 0.55], p < 0.00001, very low certainty evidence), non-significant change at 2-4 months (SMD: -0.15, CI [-0.35, 0.06], p = 0.16, very low certainty evidence), small improvement at 5-7 months (SMD: -0.47, CI [-0.64, -0.29], p <0.00001, low certainty evidence), large improvement at 8-12 months (SMD: -1.31, CI [-1.75, -0.87], p

<0.00001, low certainty evidence), and large improvement at >12 months (SMD: -1.37, CI [-2.24, -0.50], p = 0.002, low certainty evidence).

6- Boston carpal tunnel questionnaire (BCTQ)

6.1 BCTQ-Symptom Severity

The overall effect of CT release on BCTQ-Symptom Severity was large improvements compared to pre-operative levels (SMD: 3.15, CI [2.93, 3.37], p< 0.00001, I^2= 97%, 49 studies, low certainty evidence) (Figure 6.1).

There was evidence of large reductions in BCTQ-Symptom Severity at <2 months (SMD: 1.66, CI [1.42, 1.90], p <0.00001, low certainty evidence), very large reductions at 2-4 months (SMD: 2.95, CI [2.53, 3.36], p <0.00001, low certainty evidence), 5-7 months (SMD: 3.35, CI [2.97, 3.73], p <0.00001, low certainty evidence), 8-12 (SMD: 4.95 [3.95, 5.94], p <0.00001, moderate certainty evidence), and at >12 months (SMD: 5.81 [3.8, 7.82], p <0.0001, moderate certainty evidence).

6.2 BCTQ-Function

The overall effect of CT release on BCTQ-function demonstrated large improvements compared to pre-operative levels (SMD: 2.51, CI [2.29, 2.73], p< 0.00001, I^2= 98%, 49 studies, low certainty evidence) (Figure 6.2).

Combined data revealed that there was evidence of a moderate reduction in BCTQ-Function at <2 months (SMD: 1.27, CI [0.92, 1.61], p <0.00001, low certainty evidence), large reductions at 2-4 months (SMD: 2.37, CI [1.95, 2.79], p <0.00001, low certainty evidence), very large reductions at 5-7 months (SMD: 2.62, CI [2.27, 2.97], p<0.00001, low certainty evidence), 8-12 months (SMD: 3.96, CI [3.08, 4.84], p

<0.00001, moderate certainty evidence), and >12 months (SMD: 4.24, CI [2.77, 5.71], p = 0.0001, low certainty evidence).

Intraepidermal nerve fibre density (IENFD) and signs of regeneration

After 6 months post-surgery, one study showed improvement of IENFD compared to preoperative values, without any changes of Meisner corpuscles density [21]. At 12 months post-surgery, another study showed no change of IENFD, with increased density of Meisner corpuscles compared to preoperative values [163]. Both studies reported lower IENFD and myelinated axons density at 6- and 12-months post-surgery compared to healthy controls [21,163]. At 12 months post-surgery, signs of ongoing regeneration persist [163].

B- Comparison post-surgery outcomes versus healthy controls

1. Nerve conduction studies of median nerve

At 1 year post-surgery, there remained a large deficit in DML in surgically-treated patients compared with healthy individuals (SMD: 1.42, CI [0.77, 2.06], p <0.0001, low certainty evidence), a moderate deficit in CMAP amplitude (SMD: -0.72, CI [-1.02, -0.42], p <0.00001, low certainty evidence), a very large reduction in SCV (SMD: -2.28 CI [-2.91, -1.64], p <0.00001, low certainty evidence), and a large deficit in SNAP (SMD: -1.82, CI [-2.16, -1.49], p <0.00001, low certainty evidence) (Figure 7.1).

2. QST

At 4-6 months after surgery, there was evidence for no difference in most QST measures in CT release patients compared with healthy individuals; CDT (SMD: -0.32, CI [-0.64, 0.01], p = 0.05, low certainty evidence), CPT (SMD: 0.13, CI [-0.10, 0.36], p =

0.27, low certainty evidence), HPT (SMD: -0.26, CI [-0.62, 0.11], p = 0.17, low certainty evidence), PPT (SMD: 0.05, CI [-0.56, 0.65], p = 0.87, low certainty evidence), MPT (SMD: -0.04, CI [-0.34, 0.25], p = 0.77, low certainty evidence), MPS (SMD: -0.08, CI [-0.72, 0.55], p = 0.79, very low certainty evidence), TSL (SMD: 0.37, CI [-0.01, 0.75], p = 0.05, low certainty evidence), VDT (SMD: 0.37 [0.12, 0.63], p = 0.004, low certainty evidence), and WUR (SMD: -0.17 [-0.62, 0.28], p = 0.45, low certainty evidence) (Figure 8.1). Small deficits remained in WDT (SMD: 0.28, CI [0.06, 0.50], p = 0.01, low certainty evidence) and MDT (SMD: 0.59, CI [0.15, 1.02], p = 0.008, low certainty evidence).

Additional outcomes

For ulnar and radial nerves electrodiagnostic measures, there was no improvement in all outcomes except for ulnar nerve DML that showed significant improvement at 6 months post-surgery. For ulnar nerve QST, there was overall improvement of CDT and VDT post-surgery compared to pre-surgery baseline. There was no change in the autonomic measures (hand circulation) of median and ulnar nerve territories as investigated by infrared thermography. Brain function showed significant improvement 3-6 months post-surgery compared to pre-surgery baseline (See **Appendix 5**).

Discussion

We identified a gradual improvement of measures of median nerve function and structure over time. Some measures of nerve function (e.g., electrodiagnostic testing, WDT, VDT, MDT) and structure (e.g., IENFD) did not show full recovery, even after extended postoperative periods.

The improvement in all electrophysiological parameters (motor and sensory latencies, amplitudes, conduction velocities) post compared to pre-surgery suggested a

positive regeneration capacity of the median nerve following surgical decompression. These changes were already apparent for sensory parameters in the early stages after surgery (within 2 months) while motor recovery became apparent from 2 months onwards in most parameters (e.g., DML, MCV, CMP). All electrophysiological parameters showed continuous and gradual recovery over time with largest improvements at one year follow up time point or beyond.

While distal latencies and resulting conduction velocities may reflect myelin integrity, compound action potential amplitudes are often interpreted as a proxy of axonal integrity [123]. Here, changes potentially indicating remyelination were apparent early after surgery, but improvements were gradual and over a prolonged period. This is in line with experimental evidence of early yet incomplete improvements of myelin thickness two weeks after decompression of chronic compression injury [112]. Most preclinical models studying remyelination use acute nerve injuries, while our review included primarily chronic cases of CTS.

In contrast to remyelination, axonal regeneration is slower [58]. The rapid improvements in sensory compound action potential amplitudes apparent within 2 months after decompression are likely to represent resolution of ischemic conduction blocks (a well-established feature of CTS pathology) [99] rather than axon regeneration, which would be expected at later time points only. Motor amplitudes show delayed improvements; sensory and motor amplitudes continue to increase over time, consistent with expected timeframes of axonal regeneration of heavily myelinated fibres (A-alpha and A-beta^2)[177].

None of the electrodiagnostic parameters reached normal levels even at one year post surgery. The incomplete recovery of nerve conduction velocities and latencies may reflect the thinner nature of regenerated myelin [45,69]. Incomplete recovery of action potential amplitudes may indicate inadequate axonal regeneration. IENFD in skin biopsies was lower compared to healthy controls 6 and 12 months after surgery, when full reinnervation would have been expected [21,163]. The paucity of studies beyond a 5-year post-operative follow-up prevents any conclusions on whether the electrical properties of the median nerve ever completely recover following carpal tunnel surgery [40].

Recovery of somatosensory function quantified through QST, SWM, and 2PD matches a gradual improvement in detection thresholds over time (e.g., CDT, VDT, and MDT). While all detection thresholds reached levels comparable to healthy controls 4-6 months after surgery, WDT, VDT, and MDT remained impaired even at the longest follow up time points. The continuing impairment in large-fibre mediated MDT and VDT is in line with the only partial recovery of large fibre electrophysiological function. Similarly, the irreversible impairment in small-fibre mediated WDT is consistent with the failure of complete regeneration of IENFD [21,163]. In contrast to detection thresholds, pain thresholds did not change following surgery. This is likely due to unaltered pain thresholds at group level in patients with CTS compared to control participants [21,178]. Post-surgical pain thresholds were comparable to healthy control values in our data.

The functional median nerve recovery was also apparent in gradually improving grip and pinch strength postoperatively. The slight but consistent decline of pinch and grip strength within two months after surgery likely reflects factors associated with the

recent surgery such as pain inhibition, protective use or postoperative swelling limiting strength development rather than exacerbating neural motor deficits [113]. This hypothesis is supported by stable electrophysiological motor parameters which did not deteriorate at the early time point. The paucity of studies comparing grip strength post-surgery to healthy controls [32] prevent any inferences on the extent of recovery.

Previous studies have demonstrated impaired sensation not only in the median nerve territory but also in the radial and ulnar nerve territories of the hand [188]. These changes might be related to altered representation of the somatosensory cortex [187] and morphological changes (e.g., reduced ulnar nerve cross sectional area at Guyon's tunnel) associated with CTS [63]. Following surgical release, a significant improvement in DML of the ulnar nerve and VDT in the ulnar nerve territory were observed up to 6 months, in parallel with an improvement of somatosensory cortex representation and increased ulnar cross-sectional area after the same timepoint [63].

Clinical implications and recommendations for future research

Nerve structure and function gradually improved following CTS decompression surgery. However, many parameters failed to recover to the level of healthy controls. Average BCTQ ratings improved, yet on average, patients did not achieve complete symptom relief at 12 months after surgery. This might reflect subgroups of patients (e.g., mild versus severe CTS) who do not benefit from surgery; 25% of patients do not have a successful outcome and 8% are worse than before surgery [24]. Alternatively, nerve function and structure may never fully recover, even in patients with successful clinical outcome (i.e., pain and disability) [21]. Our observation of incomplete functional

and structural neuronal recovery challenges delayed provision of surgery as is currently the case in many healthcare systems with long waiting lists [1].

While our study design cannot confirm a causal effect, our findings indicate time-dependent improvement in functional and structural nerve properties following surgery. Future studies comparing the effectiveness of surgical versus non-surgical management strategies would benefit from including a range of biopsychosocial outcome measures including nerve conduction studies, QST, IENFD, 2PD, grip/pinch strength, and brain imaging for a comprehensive insight into potential benefits of surgery on neuronal health.

Limitations

Our comprehensive review identified many papers confirming functional neuronal recovery following carpal tunnel decompression (e.g., somatosensory function, electrodiagnostic parameters, hand strength). However, few studies have examined structural neuronal changes following surgery. While these studies look similarly promising (e.g., increased IENFD, improvement of resting state functional connectivity of the thalamus and primary somatosensory cortex), more studies are required to make firm conclusions about the nature and extent of nerve regeneration following CTS. Additionally, the number of healthy controls included in this study is small. Thus, the results of incomplete neural recovery should be interpreted with caution.

Thirty RCTs and 10 observational studies had high risk of bias or were of poor quality, reflecting the overall low quality of literature in the field of CTS [34]. Most meta-analyses had considerable statistical heterogeneity. The heterogeneity might be partly explained by the inclusion of different surgical techniques (e.g., open and endoscopic).

A recent systematic review comparing outcomes between open and endoscopic release reported higher heterogeneity across most outcome measures [115]. Including participants with different CTS severity or symptom durations might also contribute to the higher heterogeneity levels [127]. Exceptions to this were QST parameters, which mostly showed heterogeneity that might not be important or moderate. A likely explanation is that most QST papers followed the same validated protocol by the German Network for Neuropathic Pain [170]. To address the quality of studies and statistical heterogeneity, we included certainty of evidence rating using GRADE assessment, which takes these items into account. Most meta-analyses had low to moderate certainty evidence. Also, most meta-analyses outliers came from studies that reported median and IQR [14,40,153], and we cannot exclude the potential for mistakes in reporting.

Conclusion

We observed clear and gradual improvements in self-reported symptom and hand function, neurophysiological parameters, grip/pinch strength and somatosensory detection thresholds following carpal tunnel decompression surgery. Many parameters of nerve function and structure did not regain normal values seen in healthy controls even after prolonged periods of postoperative recovery (1 year and beyond).

Author contribution: All authors contributed to designing the project. ME and FK participated in the risk of bias assessment. SY, HL, and FK participated in data extraction. For selection of included studies, AS and AM checked the studies against eligibility criteria. All authors participated in editing and revising the manuscript. MS, RS,

KA, and AS participated in meta-analysis, writing, reviewing, and finalizing of all data. All authors read and approved the final manuscript.

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Figure legend

Fig 1 Flow diagram

Fig 2 Risk of bias assessment

Fig 3 Risk of bias domains

Fig 1.1 Distal motor latency of median nerve. CTR: carpal tunnel release, CTS: carpal tunnel syndrome.

Fig 1.2 Motor conduction velocity of median nerve. MCV: motor conduction velocity, CTR: carpal tunnel release, CTS: carpal tunnel syndrome.

Fig 1.3 Compound motor action potential of median nerve. CMAP: compound motor action potential, CTR: carpal tunnel release, CTS: carpal tunnel syndrome.

Fig 1.4 Sensory conduction velocity of median nerve. SCV: sensory conduction velocity, CTR: carpal tunnel release.

Fig 1.5 Sensory nerve action potential of median nerve. SNAP: sensory nerve action potential, CTR: carpal tunnel release, CTS: carpal tunnel syndrome.

Fig 2.1 Cold detection threshold of median nerve territories.

Fig 2.2 Warm detection threshold of median nerve territories.

Fig 2.3 Thermal sensory limen of median nerve territories.

Fig 2.4 Cold pain threshold of median nerve territories.

Fig 2.5 Heat pain threshold of median nerve territories.

Fig 2.6 Pressure pain threshold of median nerve territories.

Fig 2.7 Wind-up ratio of median nerve territories.

Fig 2.8 Vibration detection threshold of median nerve territories.

Fig 2.9 Mechanical pain threshold of median nerve territories.

Fig 2.10 Mechanical pain sensitivity of median nerve territories.

Fig 3.1 Two-point discrimination of median nerve territories. 2PD: two-point discrimination. CTR: carpal tunnel release.

Fig 3.2 Semmes Weinstein Monofilament of median nerve territories. SWM: Semmes Weinstein Monofilament, CTR: carpal tunnel release.

Fig 4.1 Grip strength. CTR: carpal tunnel release.

Fig 5.1 Pinch strength. CTR: carpal tunnel release.

Fig 6.1 BCTQ-symptom severity. CTR: carpal tunnel release, BCTQ: Boston carpal tunnel questionnaire-symptoms.

Fig 6.2 BCTQ-function score. CTR: carpal tunnel release, BCTQ: Boston carpal tunnel questionnaire-functions.

Fig 7.1 Median nerve conduction studies one year postoperative compared to healthy controls. (X) indicates the direction of postoperative improvement.

Fig 8.1 QST of median nerve territory 4-6 months postoperative compared to healthy controls. (X) indicates less postoperative improvement compared to healthy controls.

Table legend

Table 1: Quality assessment.

Table 2: GRADE assessment.

Appendices

Appendix 1: Search strategy.

Appendix 2: Study characteristics.

Appendix 3: Narrative synthesis.

Appendix 4: Funnel plots.

Appendix 5: Additional outcomes