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ORIGINAL ARTICLE

Ultrasound-guided percutaneous electrical nerve stimulation versus surgery for women with unilateral carpal tunnel syndrome: A randomized parallel-group trial

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Abstract

Objective: The aim of this clinical trial was to compare the outcomes of the application of ultrasound-guided percutaneous nerve stimulation (PENS) targeting the median nerve versus surgery for improving pain and function in women with CTS.

Methods: In this randomized parallel-group trial (ClinicalTrials.gov, NCT04246216), 70 women with CTS were randomly allocated to either PENS ($n=35$) or surgery ($n=35$) group. Hand pain intensity (mean pain and the worst pain experienced) was the primary outcome. Functional status and symptoms severity (Boston Carpal Tunnel Questionnaire, BCTQ) and self-perceived improvement (Global Rating of Change, GROC) were the secondary outcomes. Outcomes were assessed at baseline and 1, 3, 6 and 12 months after each intervention. Analysis was performed with intention to treat with mixed ANCOVAs adjusted for baseline outcomes.

Results: Analyses showed an adjusted advantage for PENS at 1 (Δ −2.0, 95% CI −2.9 to −1.1) and 3 (Δ −1.4, 95% CI −2.3 to −0.5) months for mean pain, at 1 (Δ −2.2, 95% CI −3.3 to −1.1), 3 (Δ −1.75, 95% CI −2.9 to −0.6) and 6 (Δ −1.7, 95% CI −2.8 to −0.6) months in the worst pain intensity, and at 1 (Δ −0.95, 95% CI −1.1 to −0.8), 3 (Δ −0.55, 95% CI −0.8 to −0.3) and 6 (Δ −0.4, 95% CI −0.6 to −0.8) months in function. Both groups exhibited similar changes in symptom severity. Both groups reported similar improvement at 12 months in all outcomes. Symptoms and function improved in both groups, with PENS leading to better short-term outcomes than surgery.

Conclusion: This clinical trial confirms that PENS applied with current understanding of pain mechanisms in CTS is as useful as surgery in women with CTS without denervation. The potential placebo effect of both interventions should not be ignored.

Significance: The application of percutaneous nerve stimulation was more effective at short-term, but similar effective at mid and long-term, than surgery in women with carpal tunnel syndrome.

1 | INTRODUCTION

Carpal tunnel syndrome (CTS) is the most prevalent entrapment neuropathy of the upper extremity showing an estimated lifetime prevalence of 3.1% (Pourmemari et al., 2018), although its prevalence depends on the definition used in each study (Thiese et al., 2014). Carpal tunnel syndrome is more prevalent in women and mainly affects middle-aged workers, therefore, it is associated with substantial healthcare costs and economic burden, particularly those related to loss of productivity (Foley & Silverstein, 2015).

No current consensus exists on which therapeutic option should be applied as the first-line treatment for managing people with CTS being surgery and conservative treatment approaches recommended in clinical practice guidelines (Erickson et al., 2019). These recommendations are based on the fact that differences between conservative and surgical treatments are smaller than expected (Shi et al., 2020). Several conservative interventions are proposed for the management of CTS, for example, massage, nerve gliding exercises, ultrasound, local microwave hyperthermia, transcutaneous electrical nerve stimulation (TENS), laser or hand splints (Erickson et al., 2019). Huisstede et al. (2018) found moderate evidence for most electromedical physical therapy interventions in short and mid-terms for the management of CTS.

Interventions using needles, such as acupuncture (Choi et al., 2018) or corticoid injections (Schäfer et al., 2022), have been also proposed for CTS, although their effects are still inconclusive. Percutaneous electrical nerve stimulation (PENS) consists of the application of electric current with a solid filiform needle into different musculoskeletal structures, such as tendon, ligament, muscle or nerves, with different therapeutic objectives (Deer et al., 2020). Plaza-Manzano et al. (2020) found that application of PENS showed moderately large effects on pain and a small effect on disability when applied to pain of musculoskeletal origin. However, there was a heterogeneity of tissues, for example, ligaments or muscles and locations, for example, dermatomes or painful sites, targeted with the needle (Plaza-Manzano et al., 2020). The application of PENS nearby to peripheral nerve trunks, an intervention also called percutaneous neuromodulation, has shown promising results in some musculoskeletal conditions (Fidalgo-Martin et al., 2022). However, most studies have included patients with pain of musculoskeletal origins such as low back pain or knee pain (García-Collado et al., 2022). No study investigating the effects of PENS for treatment of neuropathic pain of the upper extremity such as carpal tunnel syndrome is still available (García-Collado et al., 2022).

Carpal tunnel syndrome has been traditionally considered a peripheral neuropathy, caused by a local entrapment of the median nerve just at the carpal tunnel; however, current evidence supports that CTS is a complex syndrome associated with excitability of the central nervous system and altered conditioned pain modulation (Fernández-de-las-Peñas & Plaza-Manzano, 2018; Sobeeh et al., 2022). Most studies investigating the effects of physical therapy modalities against surgery in people with CTS applied localized interventions focused on the wrist/hand (Erickson et al., 2019; Huisstede et al., 2018; Shi et al., 2020), which does not consider the complexity of this pain condition (Fernández-de-las-Peñas & Plaza-Manzano, 2018; Sobeeh et al., 2022). The presence of altered nociceptive processing may explain the heterogeneity in the clinical outcomes observed in clinical trials. For example, Perreault et al. (2021) found that pain mechanisms are not routinely considered in trials investigating needling approaches for neuropathic pain conditions. Accordingly, the aim of this randomized clinical trial was to investigate if the application of PENS targeting the median nerve is effective for improving pain and function in women with CTS as compared to surgery. We hypothesized that women receiving PENS would exhibit similar outcomes in pain and function to those receiving surgery at short- and long-term follow-ups.

2 | METHODS

2.1 | Participants

A randomized parallel-group clinical trial was conducted. Consecutive women with a clinical (i.e., pain and paraesthesia in the median nerve distribution, increasing symptoms during the night, positive Tinel sign or positive Phalen sign) and electromyographic (i.e. according to the guidelines of the American Association of Electrodiagnosis, the American Academy of Neurology and American Physical Medicine and Rehabilitation Academy) (2002) diagnosis of CTS recruited from a local regional Hospital in Madrid (Spain) were screened for eligibility criteria. Symptoms had to have persisted for at least 6 months. Patients were classified as minimal, moderate or severe according to electromyographic findings.

Exclusion criteria consisted of: (1) presence of sensory or motor deficits in the ulnar or radial nerves; (2) adults older 65 years of age; (3) bilateral symptoms; (4) previous surgery, steroid injections or physical therapy interventions; (5) multiple medical diagnoses on the extremity (e.g., radiculopathy or myelopathy); (6) previous trauma on cervical, shoulder or extremity; (7) systemic disease

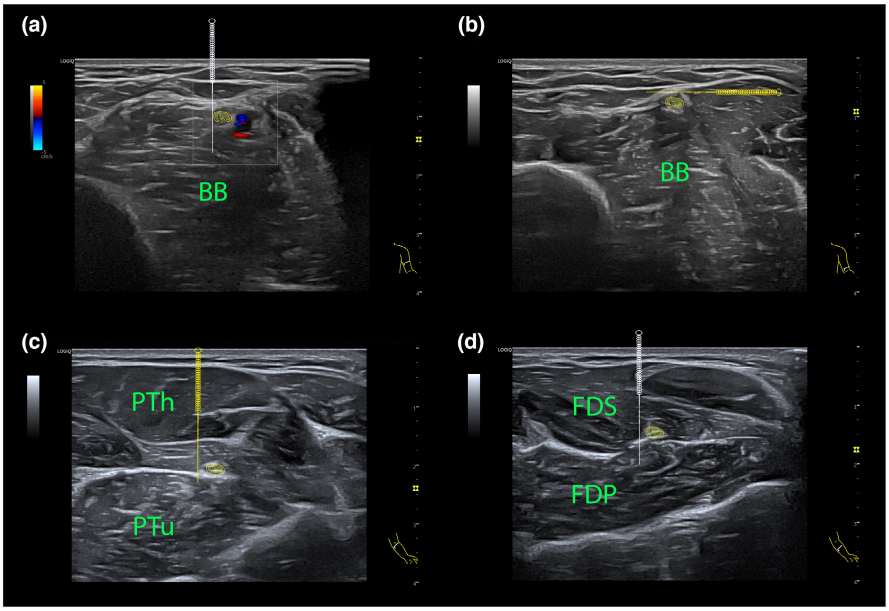

FIGURE 1 Ultrasound imaging of the arm (biceps brachii, [a] 20 cm superior to the medial epicondyle over, [b] 10 cm superior to the medial epicondyle) and forearm ([c] 3 cm inferior to the medical epicondyle; [d] 10 cm inferior to the medial line of the elbow) points for application of ultrasound-guided percutaneous electrical stimulation in the median nerve. BB, Biceps brachii muscle; FDP, flexor digitorum profundus muscle; FDS, flexor digitorum superficialis; h, humeral head; PT, Pronator teres; u, ulnar head. The circle represents the median nerve.

causing CTS (e.g., diabetes mellitus and thyroid disease); (8) any medical condition altering pain perception (e.g., fibromyalgia); (9) pregnancy; or (10) male gender. The local human research committee of the Hospital approved the study project (HUFA19/105). All subjects signed the informed consent prior to their inclusion in the trial. The protocol was prospectively registered at ClinicalTrials.gov (NCT04246216).

2.2 | Treatment allocation

Patients were randomly assigned to receive PENS or surgery. Concealed allocation was conducted using a computer-generated randomized table of numbers created with the Excel program prior to data collection. Individual and sequentially numbered index cards with the random assignment were prepared, folded and placed in sealed opaque envelopes. A researcher not involved in the recruitment or treatment of patients opened the envelope and proceeded with treatment allocation. Outcomes were assessed at baseline and 1, 3, 6 and 12 months after the end of the intervention.

2.3 | Interventions

All participants were naïve to both interventions used in the current clinical trial. Participants allocated to the experimental group received three sessions, once per week, of PENS targeting the median nerve. In regional anaesthesia, medical doctors place bevelled needles in situ during the treatment period during the application of a similar intervention (Ilfeld et al., 2017). In the current study, we applied the electrical current with solid filiform needling placed as close as possible to the median nerve. A M-MSK ultrasound system (SonoSite®) with a linear array transducer (HFL38x, SonoSite®) at 12 MHz was used to visualize the needle and to place the needle accurately and safely close to the targeted nerve. The median nerve was imaged in a transverse cross-sectional (short axis) view at 2 points on the arm and another 2 points at the forearm. The arm points were medial to the biceps brachii muscle, 20 cm (Figure 1a) and 10 cm (Figure 1b**)** superior to the medial epicondyle. The forearm points were at a point 3 cm inferior to the medial epicondyle where the median nerve passes between the humeral and ulnar heads of the pronator teres (Figure 1c); and at a point 10 cm inferior to the medial line of the elbow joint where the median nerve passes between the flexors digitorum superficialis and profundus muscles (Figure 1d). The stimulation points of the median nerve were located distant from the entrapment point (carpal tunnel) and not performed near the affected area to avoid further irritation of the nerve and provocation of symptoms.

Once the median nerve was US guided and identified at each point, the skin was cleaned with alcohol before needle insertion. We used 0.30 × 25 mm (Agupunt®) solid needles in all interventions. We confirmed nerve stimulation by visible contraction of the median nerve innervated-related musculature in response to 2–3 electric impulses (10 Hz, 1.5 mA, 240 μs) with a Pointer Plus® (UPC Medical Supplies). The needles were left in situ at the points and connected to an electrostimulator (ES-160 ITO co.) which applied a biphasic continuous waveform

at 2 Hz frequency (Hamza, White, et al., 1999) and with 250 ms pulse duration (Hamza, Ghoname, et al., 1999). The electrical current was increased at each session at an intensity of a visible motor response of the median nerve innervated musculature (around 5–6 mA) (Wang et al., 1997). This motor response was perceived non-painful by the patient.

Patients received three consecutive sessions, once/week, with both needle placements. First, the arm placement, where both needle tips were placed close to the median nerve (Figure 2a,b), was applied for 15 min. Second, the forearm placement, where both needle tips were placed close to the median nerve (Figure 2c,d), was also applied for 15 min. The third treatment session also included an educational teaching session on tendon/nerve gliding interventions for performing as homework if necessary (Núñez de Arenas-Arroyo et al., 2021). During the educational session, an experienced physical therapist explained to the patient that nerve and tendon gliding exercises targeting the median nerve (Coppieters & Alshami, 2007) need to be performed as follows. They were instructed to perform shoulder girdle depression, gleno-humeral abduction and lateral rotation and supination of the forearm, wrist, thumb and fingers extension (Coppieters et al., 2009). From that position, the patient was instructed to perform concurrent elbow flexion and wrist extension alternatively with concurrent elbow extension and wrist flexion (Coppieters & Butler, 2008). Speed and amplitude of movement should be pain free. The patients were asked to do two sets of 10 rep each with 1 min rest between sets if needed.

Patients randomly allocated to the surgery group underwent endoscopic decompression release of the carpal tunnel as this procedure results in better recovery, higher satisfaction rates and fewer scar-related complications (Li et al., 2020). All surgeons were highly experienced with at least 10 years of practice with this surgical procedure. Surgeons referred patients for hand therapy after surgery as their usual routine. Patients allocated to the surgery group also received the educational session for performing tendon and nerve gliding exercises as the PENS group.

Participants were encouraged to not modify any work or activity levels and only perform the tendon/nerve glide exercises if they experienced increases in their symptoms during the follow-up period. No other therapeutic intervention, for example, nocturnal splints, local injections or physiotherapy, was permitted from enrolment in the study to the follow-up period. Participants within the surgery group were permitted for using non-steroidal anti-inflammatory drugs (NSAID) during the first month after the intervention if needed. After the first month, no medication intake was permitted.

2.4 | Outcomes

The primary outcome of this study was the mean intensity of hand pain. No minimal clinically important difference (MCID) has yet been published for hand-related pain, but a change of 2 points or a 30% decrease in pain intensity from baseline can be considered as MCID in patients with chronic pain (Farrar et al., 2001; Salaffi et al., 2004). The mean level of pain and the worst level of pain experienced the preceding

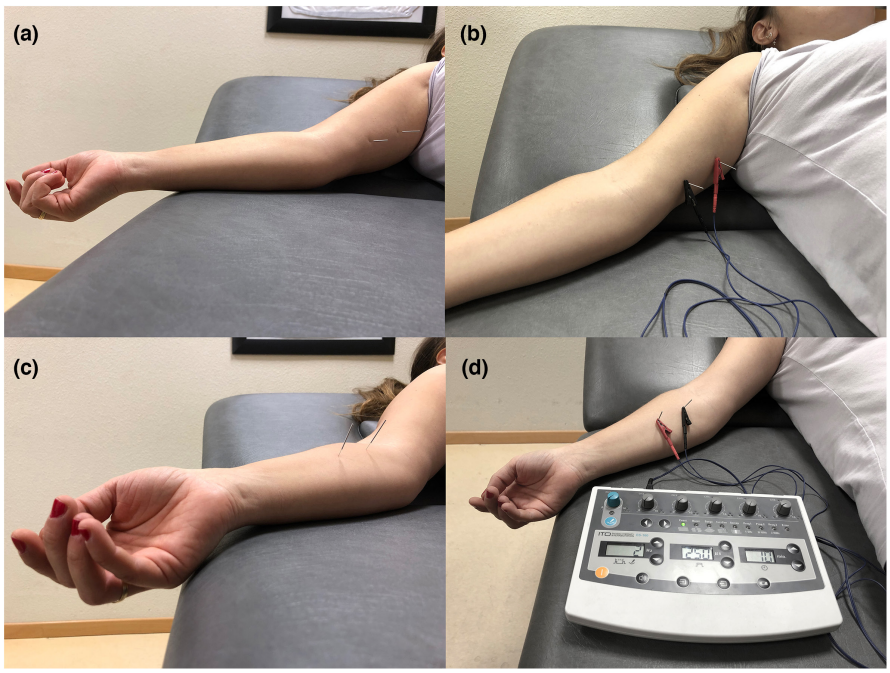

FIGURE 2 Application of ultrasound-guided percutaneous electrical stimulation on the patient on the arm (a, b) and forearm (c, d) points.

week were evaluated with an 11-point Numerical Pain Rating Scale (NPRS, 0: no pain; 10: maximum pain) (Jensen et al., 1999). We excluded the lowest level of pain from the final analysis (originally included in the clinical trial registry) because several patients reported no minimal pain from the beginning of the trial and this situation would lead to relatively 'false' improvements in this outcome.

Secondary outcomes included the functional status and symptoms severity assessed with the Boston Carpal Tunnel Questionnaire (BCTQ, score 1–5) where higher scores in the BCTQ indicate worse function and greater symptom severity (Rosales et al., 2002). Kim and Jeon (2013) proposed 0.74 points in the function scale and 1.14 points in the symptom subscale as the MCID for CTS. More recently, De Kleermaeker et al. (2019) proposed that the MCID should represent at least a change of 30% from baseline rather than a fixed cut-off point.

Finally, the self-perceived improvement was also assessed as a secondary outcome with a global rating of change (GROC) with scores ranging from −7 (a very great deal worse) to +7 (a very great deal better). Scores of +4 and +5 on the GROC suggest moderate changes in patient status, whereas scores of +6 and +7 indicate large changes in the clinical status (Wyrwich et al., 1999).

2.5 | Treatment adverse effects

Participants were asked to report any adverse event that they experienced during the intervention, after the intervention or at any part of the follow-up. In the current trial, an adverse event was defined as sequelae of short or mid-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 slightly deviated from the initial trial registry. We originally planned to recruit 100 patients; however, due to the COVID-19 pandemic restrictions during the recruiting process, we reduced the sample size. The sample size was hence calculated for detecting between-groups treatment differences of 1.5 units on the primary outcome, assuming a standard deviation of 1.75, using an a priori analysis with an F-test ANOVA for repeated measures setting a 5% of significance level ($\alpha = 0.05$), 90% of statistical power, two groups and five repeated measurements for our primary outcome. The estimated sample size was at least 30 participants per treatment group. A dropout rate of 15% was expected during the follow-up, so 35 patients were finally included in each group.

2.7 | Statistical analysis

Statistical analysis was performed using SPSS software, version 25.0 and it was conducted according to intention-to-treat analysis for patients in the group to which they were allocated. Independent student *t*-tests (continuous data) and χ^2 tests of independence (categorical data) were used to compare baseline data between both groups. Repeated-measure analyses of covariance (ANCOVA) with time (baseline, 1, 3, 6, 12 months) as the within-subject factor and group (PENS, surgery) as the between-subject factor and adjusted for baseline outcomes (including CTS severity) were conducted for evaluating between-group differences in all the outcomes. We used χ^2 tests to compare self-perceived improvement and success rates at 6 and 12 months in both groups. To enable comparison of effect sizes, the effect size was estimated using the η_p^2 if significant. Partial eta squared was used instead of Cohen's *d* since this statistical estimate is recommended in ANOVA models (Richardson, 2011). A $\eta_p^2 = 0.01$ was considered small, 0.06 medium and 0.14 large (Richardson, 2011).

3 | RESULTS

Between March 2020 and March 2021, 90 consecutive patients with CTS were screened for eligibility criteria. Seventy (77%) satisfied all inclusion criteria, agreed to participate and were randomly allocated into PENS ($n = 35$) or surgery ($n = 35$) group. Randomization resulted in similar baseline features between groups for all variables (Table 1). In patients allocated to the PENS group, one was lost at 6 months for personal reasons and another one was lost at 12 months because she received surgery on the hand. Similarly, two patients allocated to the surgical group were lost at 12 months follow-up because they received re-surgery in the hand. No patient reported any relevant adverse event during the study in either group. Figure 3 shows the flow diagram of patient recruitment and retention during the study.

Adjusting for baseline outcomes, the mixed-model ANCOVA observed significant Group*Time interactions for mean pain ($F = 7.038$; $p < 0.001$; $\eta_p^2 = 0.095$) and the worst pain ($F = 6.236$; $p < 0.001$; $\eta_p^2 = 0.084$) intensity: women with CTS receiving PENS reported higher decreases at 1 (Δ −2.0, 95% CI −2.9 to −1.1) and 3 (Δ −1.4, 95% CI -2.3 to −0.5) months in mean pain intensity (both, $p < 0.01$, Figure 4a) and at 1 (Δ −2.2, 95% CI −3.3 to −1.1), 3 (Δ −1.75, 95% CI −2.9 to −0.6) and 6 (Δ −1.7, 95% CI −2.8 to −0.6) months in the worst pain intensity ($p < 0.01$, Figure 4b) than those women receiving surgery. Between-group effect sizes were moderately favouring the PENS group. No significant differences at 6 and 12 months for mean pain intensity and at 12 months for the worst pain intensity were observed (Table 2).

TABLE 1 Baseline characteristics by treatment assignment.

	PENS group ($n=35$)	Surgery group ($n=35$)
Age (years)	46 ± 10	47 ± 7
Years with pain	3.8 ± 0.6	3.7 ± 1.4
Occupation		
Work at home *n* (%)	17 (48.5%)	16 (45.7%)
Secretary/Office *n* (%)	18 (51.5%)	19 (54.3%)
Symptoms distribution *n* (%)		
Right side	20 (57.1%)	22 (62.8%)
Left side	15 (42.9%)	13 (31.2%)
Severity *n* (%)		
Minimal CTS	10 (28.5%)	9 (25.7%)
Moderate CTS	14 (40%)	13 (37.15%)
Severe CTS	11 (31.5%)	13 (37.15%)
Mean intensity of the pain (NPRS, 0–10)	5.1 ± 1.5	5.3 ± 2.0
Worst pain experienced last week (NPRS, 0–10)	6.9 ± 1.8	7.1 ± 1.9
Function status scale carpal tunnel syndrome (1–5)	2.3 ± 0.6	2.4 ± 0.7
Severity status scale carpal tunnel syndrome (1–5)	2.5 ± 0.7	2.7 ± 0.6

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

Abbreviations: BCTQ, Boston Carpal Tunnel Questionnaire; NPRS, numerical pain rate scale; PENS, percutaneous nerve stimulation.

The intention-to-treat analysis also revealed significant Group*Time interaction for function (F = 7.129; $p = 0.009$; η_p^2=0.095), but not for symptoms severity (F = 3.350; $p = 0.072$; η_p^2=0.047) subscale of the BCTQ: women with CTS who received PENS exhibited higher increases in function at 1 (Δ −0.95, 95% CI −1.1 to −0.8), 3 (Δ −0.55, 95% CI −0.8 to −0.3) and 6 (Δ −0.4, 95% CI −0.6 to −0.8) months than those receiving surgery (Figure 4c). Between-group effect sizes were moderate in favour of the PENS group. No differences in function at 12 months between both groups were seen (Table 2). Changes in function were similar in both groups (Figure 4d), although changes at 1 month were significantly better for the PENS group (Δ −0.3, 95% CI −0.55 to −0.05, $p = 0.03$, Table 2).

Finally, self-perceived improvements assessed by a GROC were similar at all follow-up periods (1 month: $\chi^2 = 8.408$, $p = 0.298$; 3 months: $\chi^2 = 6.487$, $p = 0.484$; 6 months: $\chi^2 = 8.976$, $p = 0.254$; and 12 months: $\chi^2 = 8.915$, $p = 0.178$) in both groups.

4 | DISCUSSION

The current randomized clinical trial found that the application of US-guided PENS resulted in better short-term, but similar long-term, changes in pain, function and symptom severity than surgery in a sample of women with unilateral CTS. Both groups experienced clinically important improvements exceeding the MCID for all outcomes, particularly at 6 and 12 months. However, between groups differences did not surpass the MCID of the outcomes at any time point suggesting that both treatments had similar outcomes. Changes in the PENS group were clinically relevant from the first follow-up period, whereas changes within the surgery group needed 3 months for reaching clinical relevance. No between-group differences at 12 months were observed.

Current clinical guidelines on CTS support the use of conservative management as front-line treatment in cases of mild-to-moderate severity; however, no consensus exists on which intervention is more effective (American Academy of Orthopaedic Surgeons Work Group Panel, 2012; Erickson et al., 2019; Keith et al., 2009). Most conservative interventions exhibit short and mid-terms effects on CTS (Erickson et al., 2019; Huisstede et al., 2018; Shi et al., 2020). The meta-analysis by Shi et al. (2020) concluded that evidence comparing conservative versus surgical treatments depends on the intervention. For instance, they found that splints and steroid injections were equally effective as surgery at 3 months, but less effective at 6 months (Shi et al., 2020). These results should be considered under the premise that most conservative therapeutic approaches are based on traditional clinical reasoning that considers CTS just as a localized pathology

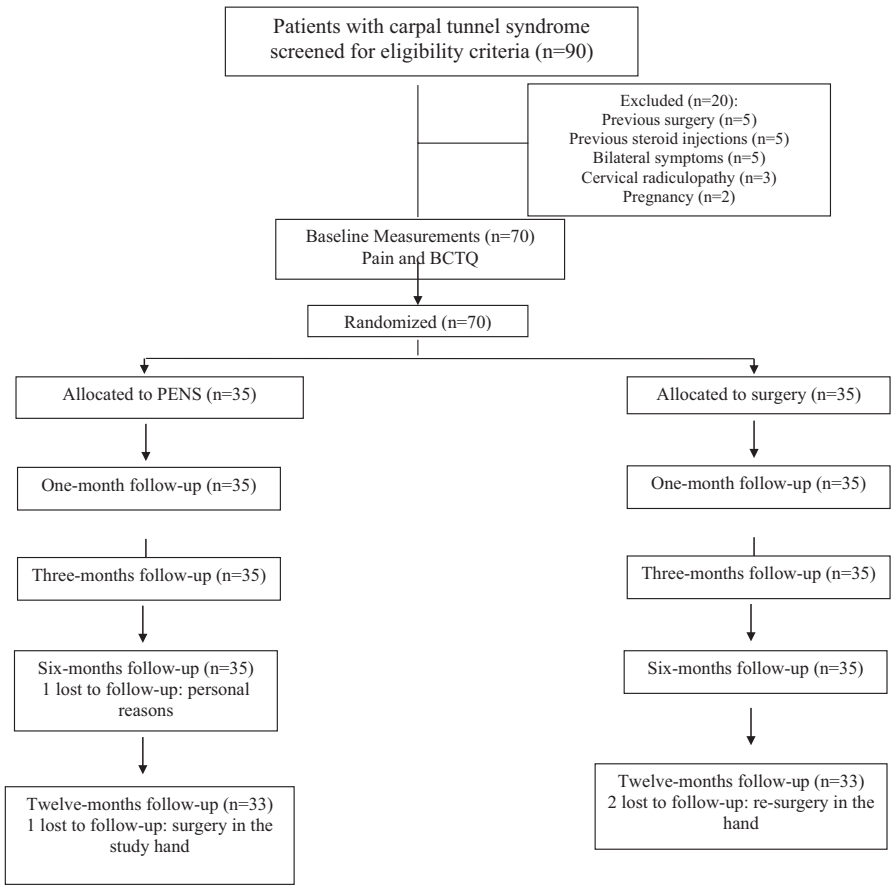

FIGURE 3 Flow diagram of patients throughout the course of the study.

associated with a lesion at the carpal tunnel and, therefore, most treatments are local, for example, splints, ultrasound, low-level laser, TENS or corticoid injections. A scoping review found that application of PENS seems to be effective for different chronic pain conditions such as low back pain, rotator cuff repair, knee pain, elbow pain or ankle instability (García-Collado et al., 2022). The current study increases evidence supporting the effects of PENS (applied to the median nerve) on a neuropathic pain condition such as CTS.

A previous clinical trial found that manual therapy, when applied using current knowledge on altered pain processing, gets better short-term and similar long-term effects at 1 year (Fernández-de-las Peñas et al., 2015) and 4 years (Fernández-de-las-Peñas et al., 2020) on pain and function as compared with surgery in women with CTS. The results observed in our trial when applying PENS were like those previously observed with manual therapy at 1-year follow-up (Fernández-de-las Peñas et al., 2015). The fact that manual therapy or PENS exhibits better short- and mid-term outcomes could be related to the fact that a disadvantage for the surgery group could be expected during some weeks or months after since any surgical approach needs time for tissue recovery. Therefore, current results add the possibility of applying PENS to patients with CTS. An important topic for discussing is that PENS was applied with solid filament needles, just placed during the treatment period and US guided for proper localization of the targeted tissue (i.e., median nerve) and for reducing the risk of puncturing the nerve (Huntoon et al., 2008). This methodology is different (i.e., less invasive) from that used by medical doctors where the electrodes are implanted close to the vicinity of the nerve for weeks or months.

It is plausible that results observed within the PENS group could have been better than with local intervention because PENS has been reported to target the nervous system. Although discussing the underlying mechanisms associated with PENS is beyond the scope of this study, some hypotheses can be proposed. First, it is possible that PENS could reduce nerve excitability (the median nerve) by altering nociceptive input and reducing neurogenic inflammation or ectopic discharge (García-Collado et al., 2022). A recent meta-analysis has concluded that PENS seems to be able to modulate altered pain processing by decreasing pain sensitivity and activating conditioning pain modulation, although further studies are needed to confirm this (Lagos et al., 2022). In fact, preliminary data suggest that manual therapy can modulate pain processing (Arribas-Romano et al., 2020). Similarly, a common underlying mechanism of PENS would explain the observed results. Nevertheless, it should be considered that PENS has an effect on relieving symptoms while surgery aims at removing nerve compression.

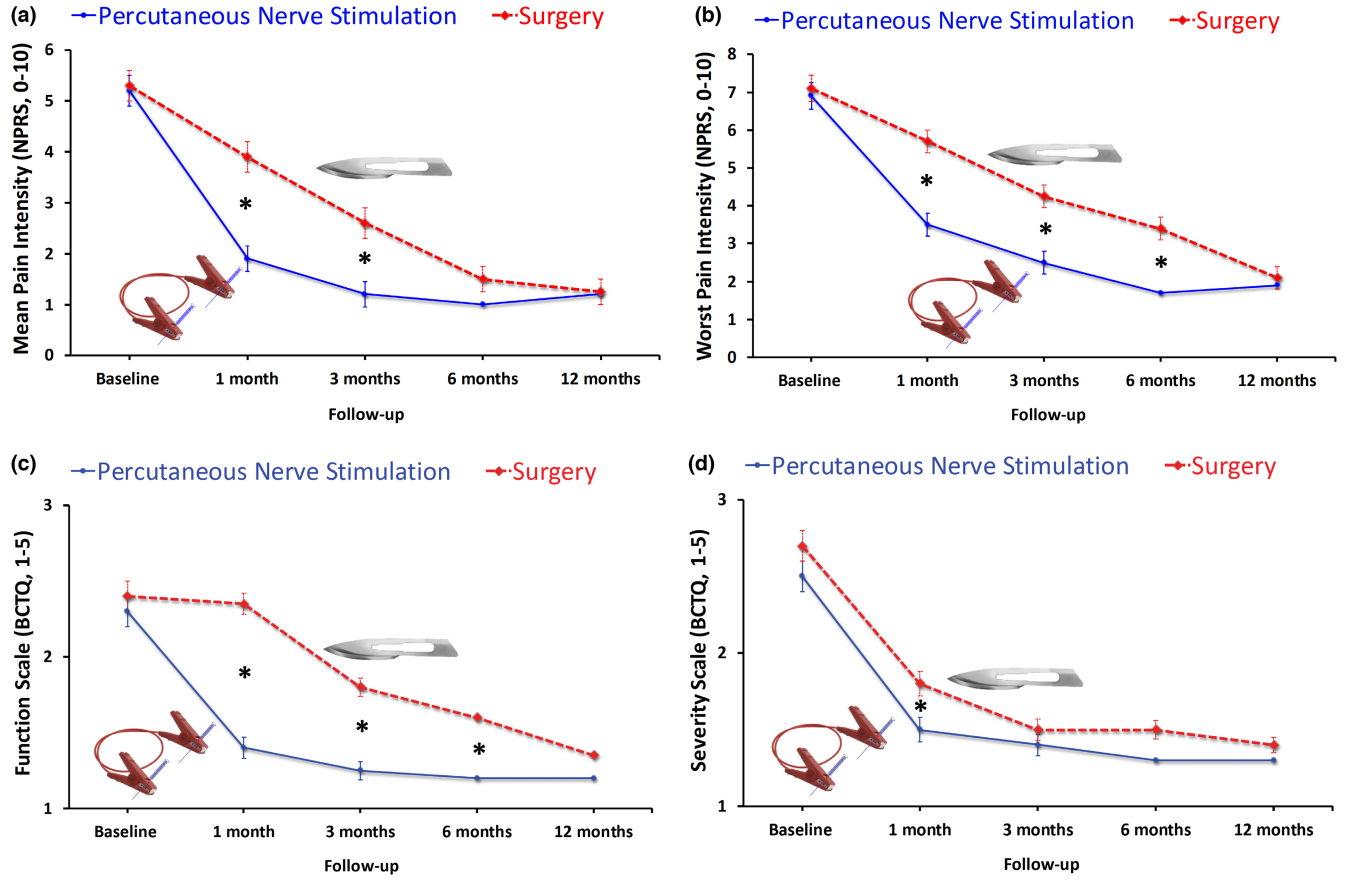

FIGURE 4 Evolution of mean pain intensity (a), the worst pain intensity (b), function (c) and symptoms severity (d) throughout the course of the study stratified by randomized treatment assignment.

TABLE 2 Primary and secondary outcomes at baseline, 1, 3, 6 and 12 months by randomized treatment assignment.

Outcome group	Baseline	1 month	3 months	6 months	12 months
Mean level of hand pain (NPRS, 0–10)					
PENS	5.1 ± 1.5 (4.5, 5.7)	1.9 ± 1.7 (1.3, 2.5)	1.2 ± 1.3 (0.6, 1.8)	1.0 ± 1.2 (0.4, 1.6)	1.2 ± 1.1 (0.6, 1.8)
Surgery	5.3 ± 2.0 (4.7, 5.9)	3.9 ± 2.2 (3.2, 4.6)	2.6 ± 2.0 (2.1, 3.1)	1.5 ± 2.1 (0.9, 2.1)	1.25 ± 1.6 (0.85, 1.65)
Worst level of hand pain experienced on preceding week (NPRS, 0–10)					
PENS	6.9 ± 1.8 (6.3, 7.5)	3.5 ± 2.2 (2.7, 4.3)	2.5 ± 1.9 (1.6, 3.4)	1.7 ± 1.9 (0.9, 2.5)	1.9 ± 1.8 (1.2, 2.6)
Surgery	7.1 ± 1.9 (6.6, 7.6)	5.7 ± 2.6 (4.9, 6.5)	4.25 ± 2.9 (3.4, 5.1)	3.4 ± 3.1 (2.5, 4.3)	2.1 ± 2.2 (1.4, 3.8)
Function subscale (BCTQ, 0–5)					
PENS	2.3 ± 0.6 (2.1, 2.5)	1.4 ± 0.35 (1.3, 1.5)	1.25 ± 0.3 (1.1, 1.4)	1.2 ± 0.2 (1.05, 1.35)	1.2 ± 0.2 (1.1, 1.3)
Surgery	2.4 ± 0.7 (2.2, 2.6)	2.35 ± 0.45 (2.2, 2.5)	1.8 ± 0.65 (1.65, 1.95)	1.6 ± 0.5 (1.5, 1.7)	1.35 ± 0.4 (1.25, 1.45)
Symptoms severity subscale (BCTQ, 0–5)					
PENS	2.5 ± 0.7 (2.3, 2.7)	1.5 ± 0.3 (1.3, 1.7)	1.4 ± 0.4 (1.25, 1.55)	1.3 ± 0.3 (1.15, 1.45)	1.3 ± 0.25 (1.2, 1.4)
Surgery	2.7 ± 0.6 (2.45, 2.95)	1.8 ± 0.6 (1.7, 1.9)	1.5 ± 0.4 (1.4, 1.6)	1.5 ± 0.45 (1.35, 1.65)	1.4 ± 0.4 (1.3, 1.5)

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

Abbreviations: BCTQ, Boston Carpal Tunnel Questionnaire; NPRS, numerical pain rate scale; PENS, percutaneous nerve stimulation.

The results of this clinical trial should be considered according to the strengths and limitations. A first strength was that we compared an effective treatment such as surgery to a well-defined novel conservative approach such as PENS. In fact, most of the participants had previously used nocturnal splints or medication for managing their symptoms, without positive effects. A second strength was that different physical therapists and surgeons were involved in both groups, supporting potential generalization of current results. Finally, the

inclusion of a long-term follow-up period increases the relevance of the study. Among the limitations, all patients were recruited from the same centre, therefore, multi-centre studies including patients from the general population would help to extrapolate better the results. Second, we did not consider the role of psychological variables, for example, depression or anxiety. Additionally, we did not evaluate patient's expectations, which could also be involved in the therapeutic process of patients with chronic pain since all patients were naïve to either intervention. Patients allocated to the PENS group received just three sessions based on the authors' clinical experience. In fact, we applied a well-defined protocol using the same frequency, duration and pulse width in all patients permitting replication of the study. We do not know if a greater number of sessions or different PENS parameters would reveal differences between the interventions. Finally, the lack of a control group not receiving any treatment (i.e., wait and see) does not permit us to exclude the potential placebo effect of both treatments. Future clinical trials should compare the effects of the proposed PENS approach against placebo.

5 | CONCLUSIONS

In conclusion, these data indicate that application of PENS targeting the median nerve was more effective in short term, but equally effective in long term, than surgery for improving pain and function in women with unilateral CTS. Our results would support the use of conservative treatment as the first management option for patients with CTS before considering surgery since both interventions are equally effective in long term.

AUTHOR CONTRIBUTIONS

All authors contributed to the study concept and design. César Fernández-de-las-Peñas and José L. Arias-Buría did the main statistical analysis. César Fernández-de-las-Peñas, Ricardo Ortega-Santiago, Ana I. De-la-Llave-Rincón and Joshua A. Cleland contributed to analysis and interpretation of data. César Fernández-de-las-Peñas and Joshua A. Cleland contributed to draft of the report. JAP and HFS provided administrative, technical and material support. Juan A. Pareja, Homid Fahandezh-Saddi Díaz and José L. Arias-Buría supervised the study. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

No conflict of interest is declared by the authors.

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