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Clinical Research Article

Neuromodulation of the median nerve in carpal tunnel syndrome, a single-blind, randomized controlled study

Gevher Rabia Genç Perdecioğlu[1], Mehlika Panpallı Ateş[2], Damla Yürük[1], and Ömer Taylan Akkaya[1]

[1]Department of Algology, Etlik City Hospital, Ankara, Turkey
[2]Departmant of Neurology, Etlik City Hospital, Ankara, Turkey

ABSTRACT

Background: This study aimed to evaluate the efficacy of pulsed radiofrequency applied using transcutaneous electrodes in carpal tunnel syndrome (CTS).
Methods: After randomization, the patients received two cycles of noninvasive pulsed radiofrequency (NiPRF), once weekly, or splinting (the control group) for three months. Clinical evaluations were recorded at baseline and weeks 4 and 8. The Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) was used to determine the functional status and symptom severity.
Results: Sixty-two patients were followed up for three months. There was no difference between the groups in the BCTQ scores before and after treatment. The NiPRF group found a significant difference between the BCTQ measurements at all time intervals (paired sample *t*-test; $P < 0.001$). In the splint group, there was a significant difference only between the basal-1st month and basal-3rd month (paired samples *t*-test; $P < 0.001$). The main effect of the time variable was statistically significant (ANOVA; $P < 0.001$), but the group variable was not. There was no correlation between the BCTQ results measured at any time and the electroneuromyelograghy findings in either group.
Conclusions: NiPRF effectively improves symptoms and functionality in patients with CTS for up to 3 months. Thus, NiPRF can be considered an easy, safe, and useful alternative treatment modality for CTS.

Keywords: Carpal Tunnel Syndrome; Chronic Pain; Median Neuropathy; Neuralgia; Pain Management; Pulsed Radiofrequency Treatment; Randomized Controlled Trial; Splints.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common compressive neuropathy and is defined as median nerve compression under the transverse carpal ligament. Female sex, pregnancy, and obesity are considered possible risk factors. It manifests as numbness, tingling, or burning in the second and third fingers and palm and is usually exacerbated at night [1].

In treatment, oral anti-inflammatory, analgesic, immobilization *via* splinting, physical and occupational therapies, oral corticosteroids, ultrasound, and interventional methods include corticosteroid injection and median nerve decompression are employed [2].

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Correspondence: Gevher Rabia Genç Perdecioğlu
Department of Algology, Etlik City Hospital, Varlık Avenue, Halil Sezai Erkut Street Etlik Keçiören/ANKARA 06170, Turkey
Tel: +90 5332009184, Fax: +90 03125962000, E-mail: gevhergenc@gmail.com

Splinting is the first treatment step. It reduces pressure in the carpal tunnel by inhibiting wrist flexion and fixing the wrist in a neutral position [3]. The American Academy of Orthopedic Surgeons recommends immobilization (corset/splint/orthosis) as a first-line treatment (strong evidence) [4].

Pulsed radiofrequency (PRF) is an effective interventional pain management technique. PRF relieves pain without causing nerve damage, unlike traditional radiofrequency (RF) applications that conduct heat up to 42°C and apply a constant high temperature of 60°C–80°C [5]. PRF is a neuromodulatory method, although the exact mechanism of action remains unclear. It causes a change in neural cellular substrates by eliciting electric field effects such as electrolyte balance and current density [6]. As a result of changes in ion channels, excitatory amino acids, and microglial activity, inflammatory cytokines are suppressed, and endogenous opioids increase[7,8]. In diabetic neuropathic rodents, PRF decreases glutamate levels in synaptic terminals [9]. Consequently, hyperalgesia and allodynia decreased with PRF.

Experience with noninvasive pulsed radiofrequency (NiPRF) in CTS has been limited in the literature. It is recommended for use in cases that do not respond to local corticosteroids [2]. Recent data have shown that PRF effectively affects compressive neuropathy of the median nerve [10–12].

In the NiPRF method, the electrodes transmit RF current through the skin to neural tissues. It is advantageous as a noninvasive and easily applicable method. NiPRF is effective for knee and shoulder pain as well as for headache [13–18].

This study aimed to evaluate the efficacy of NiPRF in patients with CTS. Pain scores were compared over time in patients who underwent NiPRF and splinting. The results show that NiPRF is an effective treatment for improving symptoms and function in CTS. Thus, NiPRF may be considered a new and safe therapeutic option for treating CTS.

MATERIALS AND METHODS

This study was a single-blind, randomized, controlled trial. Approval of Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee was obtained on 28.06.2021 (Decision no: 114/13, Clinical Trial Register Number: NCT05500079). A computer-assisted randomization program was used to categorize the patients into groups. Data were collected by researchers who managed the treatment and control process. They passed the patient records, without specifying the type of treatment, as group 1 and group 2 to the blinded investigator who analyzed the data.

1. Participants

From December 2022 to March 2023, 96 adult patients with CTS confirmed by electromyography were admitted to the outpatient pain clinic. The sample size was based on primary outcomes and calculations performed with the G*Power 3.1.9.4 software program [19,20] with an effect size of 0.854, $\alpha = 0.05$, and power of $(1 - \beta) = 0.95$. A total of 36 individuals were included in each group. In this analysis, the fourth week visual analogue scale (VAS) scores (mean and standard deviation) of the study by Chen et al. [11] was used for the sample size calculation of this study.

Inclusion criteria were age between 18–65 years, diagnosis of CTS confirmed by electroneuromyelography (ENMG), and body mass index of 20–45. The exclusion criteria were severe tenor region atrophy, pregnancy, malignancy, previous median nerve surgery/trauma, steroid injection into the median nerve within six months, and polyneuropathy.

The study design is depicted in **Fig. 1**.

2. Intervention

Transcutaneous electrodes were applied in the NiPRF group and a neutral wrist splint in the control group. For NiPRF treatment, a transcutaneous electrode-compatible PRF generator (TOP Lesion Generator; model: TLG-10) and 44 × 98 mm neurostimulation electrodes (TCPRF/TCSTP Transcutaneous Electrode; TOP Corporation; FIAB SPA Italy) were used. These electrodes were placed on the volar and dorsal wrists, as shown in **Fig. 2**. Patients received 80 volts with two pulses per second during treatment and 20 ms PRF current for 8 minutes. This treatment was repeated twice, with a one-week interval between the sessions.

A neutral wrist splint was prescribed to each participant for splinting. The patients were asked to wear the splint every night for 6 hours and at active times of the day for 12 weeks.

3. Outcome measurements

The primary outcome was the detection of temporal changes and the main effect of the group and time on

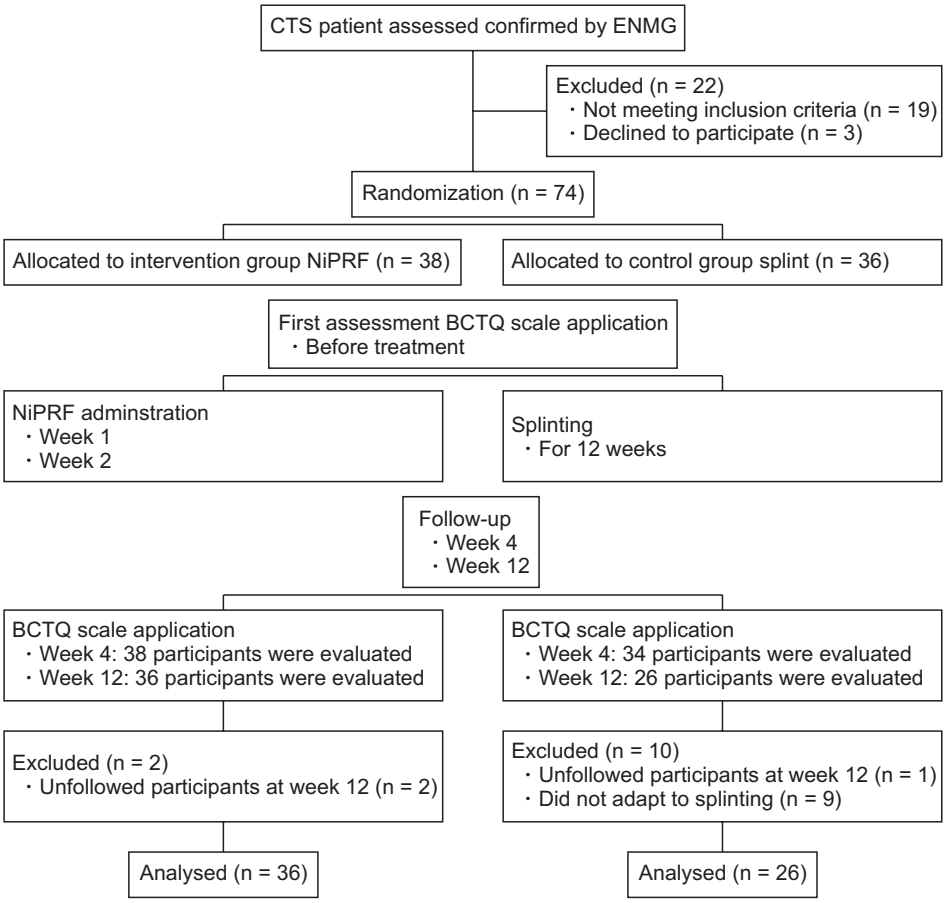

Fig. 1. Flowchart diagram. CTS: carpal tunnel syndrome, ENMG: electroneuromyelography, NiPRF: noninvasive pulsed radiofrequency, BCTQ: Boston Carpal Tunnel Syndrome Questionnaire.

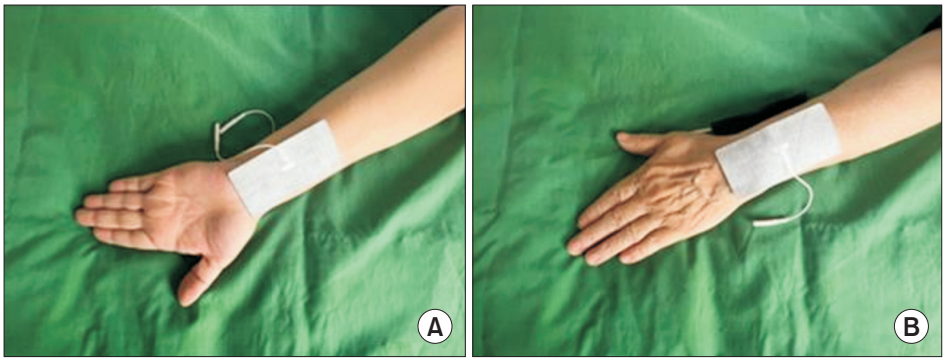

Fig. 2. Localization of the transcutaneous patch administration. (A) Volar wrist electrode application. (B) Dorsal wrist electrode application.

Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) scores. Patients' symptoms and functionalities were evaluated using the BCTQ scores before as well as 1 and 3 months after treatment. The results were statistically compared between the two groups. The main effect of the treatment group and time variables were analyzed, and the difference between the times was evaluated using comparative statistics. The secondary outcome was to assess the correlation between ENMG and BCTQ scores before and after treatment. All patients were classified as having mild-moderate-severe CTS by ENMG before treatment. Correlation analysis between the BCTQ baseline – BCTQ 1st month change and BCTQ baseline – BCTQ 3rd month change were performed.

4. Statistical analyses

All analyses used the Jamovi project (2022, Jamovi Version 2.3, Computer Software). The findings of this study are expressed as frequencies and percentages. Normal-

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Table 1. Demographic values and comparison statistics

Variable	NiPRF (n = 36)		Splint (n = 26)		Test stat	*P* value
Age	49.22 ± 11.66	49 (19–70)	48.26 ± 9.02	47.50 (32–70)	1.27	0.207[a]
Sex						
Female	29 (80.6)		18 (69.2)			0.370[b]
Male	7 (19.4)		8 (30.8)			
ENMG						
Mild	13		4			0.125[b]
Moderate	21		18			
Severe	2		4			
BCTQ scores						
Basal	60.13 ± 15.06	60 (23–86)	55.03 ± 16.13	52.50 (30–83)	1.27	0.207[a]
1 mo	34.38 ± 12.93	30.50 (15–66)	41.73 ± 17.95	39 (11–82)	–1.87	0.066[a]
3 mo	43.11 ± 17.41	42.50 (15–81)	41.76 ± 15.68	39.50 (14–82)	0.31	0.756[a]

Values are presented as mean ± standard deviation, median (min-max), number (%), or number only.
NiPRF: noninvasive pulsed radiofrequency, ENMG: electroneuromyelography, BCTQ: Boston Carpal Tunnel Syndrome Questionnaire.
[a]Independent samples *t*-test, [b]Chi-square Fisher exact test.

ity analysis was performed using the Shapiro–Wilk test, skewness kurtosis, and histograms. Normally distributed variables are presented as means and standard deviation (SD). Categorical variables were compared using the chi-squared test. Numerical dependent variables were compared between the groups using an independent sample *t*-test. Repeated measures with normal distribution, such as the BCTQ scores, were analyzed using a two-way analysis of variance (ANOVA). The correlation was analyzed with bivariate Pearson and Sperman's correlation coefficient tests. Statistical significance was set at $P < 0.05$.

RESULTS

Sixty-two patients completed the third month of follow-up in this study. Twelve patients were excluded from the study. Nine patients reported mild hyperemia during the study period in the NiPRF group.

Table 1 shows that the two groups' demographic data and baseline, first- and third-month BCTQ scores were comparable.

There was no difference in age or sex between the two groups (independent samples *t*-test, chi-square test). Each group had similar pre-treatment BCTQ scores ($P = 0.207$; independent sample *t*-test).

We compared the BCTQ scores at baseline and at the first and third months after treatment, within and between the two groups. The independent samples *t*-test, paired samples test, and ANOVA were used for analysis.

1. Primary outcome

The change in the BCTQ scores over time was evaluated. In the NiPRF group, a 43% decrease in scale score was observed in the first month and a 28% decrease in the third month. There was a statistically significant difference between the BCTQ scores measured three times in the NiPRF group (mean BCTQ 0–1 month: 25.02, 0–3 month: 16.70, 1–3 month: –8.32, $P < 0.001$; paired samples test).

In the splint group, according to the BCTQ score, a 25% reduction was observed in the first and third months. There was a statistically significant difference between the BCTQ scores measured at baseline and in the third month. Nevertheless, no difference was detected at the first and third months in the splint group (mean BCTQ 0–1 month: 13.30, 0–3 month: 13.26, 1–3 month: –0.03; $P < 0.001$, $P < 0.001$, $P = 0.974$; paired samples test).

No significant difference was found between the two groups in the BCTQ scores at any time point (independent sample *t*-test).

The Generalized Linear Model and ANOVA were used to analyze the main effects of time and group variables on BCTQ change. The main effect of time was found to be statistically significant (Wald $\chi^2 = 5.258$, SD = 2, $P < 0.001$). The group variable had no significant effect on the change in the main BCTQ. In other words, there was no significant difference between the groups (Wald $\chi^2 = 0.017$, SD = 1, $P = 0.897$) (**Table 2**).

The main effect of time on BCTQ change was significant, and the BCTQ scores measured at three different

Table 2. Analysis the main effect of group and time variables on BCTQ scores

Variable	Wald χ^2	SD	*P* value
Group	0.017	1	0.897
Time	5.258	2	< 0.001
Group * Time	5.067	2	0.079

Wald chi-square test. Dependent variable is BCTQ scores. Intercept model: Group, Time, Group * Time.
BCTQ: Boston Carpal Tunnel Syndrome Questionnaire, SD: standard deviation.

Table 3. Analysis of changes in BCTQ scores by the time between groups

Variable	BCTQ	F	*P* value	Partial Eta squared
Time	Basal–1 mo	198.41	< 0.001	0.768
	1 mo–3 mo	15.6	< 0.001	0.206
Time * Group	Basal–1 mo	20.13	< 0.001	0.251
	1 mo–3 mo	15.33	< 0.001	0.204

Two-way repeated measures ANOVA.
BCTQ: Boston Carpal Tunnel Syndrome Questionnaire, Group: noninvasive pulsed radiofrequency or splint group.

Table 4. Multiple comparison analysis between times

BCTQ time	Mean difference	Standard error	*P* value
Basal–1 mo	19.529	1.386	< 0.001
1 mo–3 mo	15.149	1.426	< 0.001
2 mo–3 mo	–4.380	1.109	0.001

Adjustment for multiple comparisons: Bonferroni.
BCTQ: Boston Carpal Tunnel Syndrome Questionnaire.

times were compared using multiple comparison tests. There was a difference of 19.529 between the pre-treatment and first-month post-treatment BCTQ scores, and the pre-treatment BCTQ score was higher than that in the first month. This difference was statistically significant ($P < 0.001$). There was a difference of 15.149 between the pre-treatment and third-month BCTQ scores; again, the first-month measurements were higher. This difference was statistically significant ($P < 0.001$). The decreases obtained in the first- and third-month BCTQ measurements after treatment were statistically significant. When the first- and third-month BCTQ scores were compared, there was a difference of 4.380, and the second-month scores were low. This difference was also statistically significant ($P = 0.001$) (based on estimated marginal means and Bonferroni corrections) (**Tables 3, 4**).

2. Secondary outcome

There was no correlation between BCTQ baseline measurements and ENMG results of patients before treatment (Pearson's $P = 0.115$). No correlation was found between the BCTQ baseline-BCTQ 1st month changes, BCTQ baseline-BCTQ 3rd month changes, and ENMG in either group (NiPRF group: Spearman's correlation, $P = 0.347$ and 0.497, Splint group: Sperman, $P = 0.769$ and 0.061).

DISCUSSION

To the authors' knowledge, this is the first report of an NiPRF treatment for CTS. The results in the NiPRF group were similar to those in the splint group. The splint was chosen for the control group because it is a method with a strong level of evidence recommended in first-line care [4,21].

The effectiveness of NiPRF in pain management was first discussed in a case report [13]. Taverner et al. [14–16] reported favourable results for treating knee and shoulder pain . Stal examined headaches in a case series [17]. Recently, Lin et al. [18] compared NiPRF and transcutaneous electrical nerve stimulation methods for managing shoulder pain. All studies reported significant improvements in pain scores within the first month after treatment; however, the third-month results varied [14–16,18].

The advantage of NiPRF is that it is noninvasive, painless, and easily applicable. No statistically significant difference was found between the decrease in BCTQ scores of patients who wore a splint every night for three months and patients who received only two 8-minute NiPRF treatments. Although the difference was not statistically significant, the decrease in the BCTQ scores in the NiPRF group was more significant than that in the splint group.

During the study period, nine patients left the control group because they could not fully adapt to splinting and switched to different treatment methods. In the NiPRF group, all patients participated in the treatment sessions, but only two patients could not be reached for the third-month control and were excluded from the data pool. Although splinting is an effective treatment without side effects, especially in the short term, it may cause patient non-compliance owing to the discomfort it creates. With NiPRF, only nine patients had mild hyperemia and did not require treatment. The patient did not experience any

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tolerance problems.

Recently, articles have focused on PRF treatment with needle electrodes applied to the median nerve. Haider et al. [10] applied ultrasound-guided PRF to the median nerve and reported a 70% reduction in pain over a 12-week follow-up period. Chen et al. [11] treated one group with PRF and splinting and the other with splinting only. Significant improvements in VAS and BCTQ scores were detected in the intervention group at all follow-up periods compared with the controls. Celenlioglu et al. [12] compared steroid injection and PRF in CTS and found no differences between the two groups.

Electrophysiological evaluation is necessary to classify and differentially diagnose CTS. BCTQ assesses symptom severity and functionality and is easy to apply. The correlation between these two tests has been previously studied, and in the literature, three studies found no correlation between ENMG and BCTQ, one study found a weak correlation, and one study found a significant correlation [22–26].

Our results were in line with the literature. There was no correlation between baseline BCTQ scores and ENMG. There was also no correlation between the rate of improvement in BCTQ scores after treatment and the ENMG. In other words, neither the symptoms' severity nor the treatment response correlated with ENMG findings.

As mentioned above, PRF produces neuromodulation by several mechanisms in the central and peripheral nervous system [7]. If the device is compatible, PRF currents from the same transducer can be delivered to the tissue *via* needle or transcutaneous electrodes [13–18]. Because the needle electrode is inserted into deeper tissue, it can reach deep nerves. However, transcutaneous electrode PRF may have a higher potential in peripheral neuropathies where nerves are superficial.

This study had several limitations. First, the patients were followed up for three months. No data was obtained to evaluate its long-term effectiveness. Second, the number of applications is small. The authors could not determine whether there was proportionality between the number of applications and effectiveness. Third, a possible placebo effect of NiPRF due to the absence of a placebo group block cannot be excluded.

In conclusion, NiPRF treatment can provide pain relief and functional improvement for up to three months in patients with CTS. The advantages of this method are that it is a noninvasive, safe, and easy-to-apply method that provides pain relief for up to 3 months with only two applications. More studies are needed for NiPRF to take its place in treatment protocols.

DATA AVAILABILITY

Data files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/2M1NDR.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

No funding to declare.

AUTHOR CONTRIBUTIONS

Gevher Rabia Genç Perdecioğlu: Methodology; Mehlika Panpallı Ateş: Formal analysis; Damla Yürük: Investigation; Ömer Taylan Akkaya: Supervision.

ORCID

Gevher Rabia Genç Perdecioğlu, https://orcid.org/0000-0002-5174-9500
Mehlika Panpallı Ateş, https://orcid.org/0000-0002-9744-9255
Damla Yürük, https://orcid.org/0000-0002-0799-3434
Ömer Taylan Akkaya, https://orcid.org/0000-0002-4559-1209

REFERENCES

1. Ostergaard PJ, Meyer MA, Earp BE. Non-operative treatment of carpal tunnel syndrome. Curr Rev Musculoskelet Med 2020; 13: 141-7.
2. Patijn J, Vallejo R, Janssen M, Huygen F, Lataster A, van Kleef M, et al. Carpal tunnel syndrome. Pain Pract 2011; 11: 297-301.
3. Huisstede BM, Hoogvliet P, Franke TP, Randsdorp MS, Koes BW. Carpal tunnel syndrome: effectiveness of physical therapy and electrophysical modalities. An updated systematic review of randomized controlled trials. Arch Phys Med Rehabil 2018; 99: 1623-34.e23.
4. Graham B, Peljovich AE, Afra R, Cho MS, Gray R,

Stephenson J, et al. The American Academy of Orthopaedic Surgeons Evidence-Based Clinical Practice Guideline on: management of carpal tunnel syndrome. J Bone Joint Surg Am 2016; 98: 1750-4.
5. Chua NH, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications-a review. Acta Neurochir (Wien) 2011; 153: 763-71.
6. Cosman ER Jr, Cosman ER Sr. Electric and thermal field effects in tissue around radiofrequency electrodes. Pain Med 2005; 6: 405-24.
7. Sam J, Catapano M, Sahni S, Ma F, Abd-Elsayed A, Visnjevac O. Pulsed radiofrequency in interventional pain management: cellular and molecular mechanisms of action - an update and review. Pain Physician 2021; 24: 525-32.
8. Lin FY, Huang KF, Chen JC, Lai MF, Ma KH, Yeh CC. The clinical application of pulsed radiofrequency induces inflammatory pain via MAPKs activation: a novel hint for pulsed radiofrequency treatment. Int J Mol Sci 2021; 22: 11865.
9. Huang YH, Hou SY, Cheng JK, Wu CH, Lin CR. Pulsed radiofrequency attenuates diabetic neuropathic pain and suppresses formalin-evoked spinal glutamate release in rats. Int J Med Sci 2016; 13: 984-91.
10. Haider N, Mekasha D, Chiravuri S, Wasserman R. Pulsed radiofrequency of the median nerve under ultrasound guidance. Pain Physician 2007; 10: 765-70.
11. Chen LC, Ho CW, Sun CH, Lee JT, Li TY, Shih FM, et al. Ultrasound-guided pulsed radiofrequency for carpal tunnel syndrome: a single-blinded randomized controlled study. PLoS One 2015; 10: e0129918.
12. Celenlioglu AE, Unal-Artık HA, Guler G. Comparison of ultrasound-guided pulsed radiofrequency versus steroid injection in the treatment of carpal tunnel syndrome. Ir J Med Sci 2022; 191: 2751-7.
13. Balogh SE. Transcutaneous application of pulsed radiofrequency: four case reports. Pain Pract 2004; 4: 310-3.
14. Taverner MG, Ward TL, Loughnan TE. Transcutaneous pulsed radiofrequency treatment in patients with painful knee awaiting total knee joint replacement. Clin J Pain 2010; 26: 429-32.
15. Taverner MG, Loughnan TE, Soon CW. Transcutaneous application of pulsed radiofrequency treatment for shoulder pain. Pain Pract 2013; 13: 310-5.
16. Taverner M, Loughnan T. Transcutaneous pulsed radiofrequency treatment for patients with shoulder pain booked for surgery: a double-blind, randomized controlled trial. Pain Pract 2014; 14: 101-8.
17. Stall RS. Noninvasive pulsed radio frequency energy in the treatment of occipital neuralgia with chronic, debilitating headache: a report of four cases. Pain Med 2013; 14: 628-38.
18. Lin ML, Chiu HW, Shih ZM, Lee PY, Li PZ, Guo CH, et al. Two transcutaneous stimulation techniques in shoulder pain: transcutaneous pulsed radiofrequency (TPRF) versus transcutaneous electrical nerve stimulation (TENS): a comparative pilot study. Pain Res Manag 2019; 2019: 2823401.
19. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007; 39: 175-91.
20. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009; 41: 1149-60.
21. Weiss ND, Gordon L, Bloom T, So Y, Rempel DM. Position of the wrist associated with the lowest carpal-tunnel pressure: implications for splint design. J Bone Joint Surg Am 1995; 77: 1695-9.
22. Sançmış M, Cavit A, Çakıcı İ, Özcanlı H, Uysal H. Is Boston questionnaire an alternative to electromyography for evaluation of the surgical outcome for carpal tunnel syndrome? Turk J Phys Med Rehabil 2020; 66: 336-42.
23. Chan L, Turner JA, Comstock BA, Levenson LM, Hollingworth W, Heagerty PJ, et al. The relationship between electrodiagnostic findings and patient symptoms and function in carpal tunnel syndrome. Arch Phys Med Rehabil 2007; 88: 19-24.
24. Bulut T, Sener U, Yağdi S, Kazimoğlu C, Sener M. Relationship between clinical and electrophysiological results in surgically treated carpal tunnel syndrome. Eklem Hastalik Cerrahisi 2011; 22: 140-4.
25. Schrijver HM, Gerritsen AA, Strijers RL, Uitdehaag BM, Scholten RJ, de Vet HC, et al. Correlating nerve conduction studies and clinical outcome measures on carpal tunnel syndrome: lessons from a randomized controlled trial. J Clin Neurophysiol 2005; 22: 216-21.
26. Almigdad A, Odat M, Almanasir G, Megdadi N, Sharadgeh S. Carpal tunnel syndrome: correlation of the severity of the clinical picture and electrophysiological studies. Arch Hand Microsurg 2023; 28: 16-23.