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Extracorporeal shock wave therapy and ultrasound therapy improve pain and function in patients with carpal tunnel syndrome. A randomized controlled trial

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Background. **Ultrasound (US) therapy improves symptoms in carpal tunnel syndrome (CTS) patients. Extracorporeal shock wave therapy (ESWT) uses acoustic energy to determine its clinical effects, as US-therapy does.**
Aim. **The aim of this study was to compare the short-term efficacy of US and ESWT on mild and moderate CTS.**
Study design. **Randomized controlled trial.**
Setting. **University outpatient service.**
Population. **Twenty-five patients with mild to moderate CTS, for a total of 42 wrists.**
Methods. **patients were randomized to receive US, cryo-US or ESWT, and were evaluated for pain and function before treatment started, at the end of treatment, and four and 12 weeks after the end of the treatment.**
Results. **Significant improvement was noted in all groups for pain (P<0.05) and functionality (P<0.05). Patients in ESWT group show greater pain improvement at 12-weeks follow-up when compared with both US and cryo-US groups (P<0.05).**
Conclusion. **Patients affected by CTS might benefit from the application of US, cryo-US or ESWT. Benefits persist 3 months after the end of treatment.**
Clinical Rehabil Impact. **Clinicians might consider the possibility of a short-term non-surgical management for mild-to-moderate CTS.**

KEY WORDS: Carpal tunnel syndrome - Ultrasonic therapy - High-energy shock waves - Physical therapy modalities.

Carpal Tunnel Syndrome (CTS) is the most frequent entrapment neuropathy in the general population.[1] This syndrome may result in substantial disability owing to a sensory and/or motor deficit in the hand and a consequent loss of hand function.

In CTS, the median nerve is compressed at the wrist. In particular, increased interstitial pressure in the carpal tunnel,[2-4] may reduce the epineural blood flow in the median nerve, thereby causing a progressive decline in its functioning.

Treatment options for CTS may be surgical or non-surgical. Although surgical treatments have been reported to yield better results than non-surgical treatments,[5] there is also strong evidence supporting the use of conservative treatments, particularly physical therapy treatments, in the management of CTS symptoms. Frasca *et al.*[6] demonstrated, in a study conducted on 34 wrists with idiopathic CTS, an improvement in both pain and function after six sessions of hyperthermia compared with a sham therapy. Moreover, high-intensity laser therapy has been found to improve both pain and paresthesias, as well as neurophysiological parameters, to a greater extent than transcutaneous electrical stimulation.[7] The role of therapeutic

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ultrasound (US) in the management of CTS has also been studied extensively. Therapeutic US appears to be more effective than either sham therapy[8] or laser therapy[9] in both symptoms relief and improvement in neurophysiological parameters in mild to moderate CTS. However, recently a meta-analysis pointed out that evidence suggesting that therapeutic US is more effective than placebo and other non-surgical interventions in people with CTS is based on very limited data.[10] Cryo-US represents a new physical therapy treatment in which the US are delivered at 0° C, in order to combine the benefits of US with those of cryo-therapy.[11] Cryo-US therapy has been successfully used for musculoskeletal conditions,[11, 12] but to date it has never been tested on CTS. A relatively new therapy reported to be of value in the treatment of CTS is extracorporeal shock wave therapy (ESWT).[13] In a group of 36 patients with CTS, a single session of 1000 shots of ESWT was found to be as effective as a single corticosteroid injection in relieving symptoms and improving nerve conduction.[14]

However, it would be interesting to determine whether ESWT is more effective in the management of CTS than other physical therapy treatments. Given the similar physical energy used in US (sound waves) and the existing, albeit apparently poor, evidence regarding its effectiveness in this neuropathy, US may be deemed a treatment modality that is suited to a comparison with ESWT in CTS patients.

In this paper, we present the results of a randomized controlled trial designed to investigate any differences between three different physical therapies, *i.e.* US, ESWT and cryo-US, in relieving symptoms in a group of patients affected by CTS in a short-term period.

Materials and methods

Subjects of both sexes, aged between 25 and 70 years, referring to our outpatient service between January 2012 and June 2012 with a diagnosis of CTS confirmed by standard nerve conduction studies, were considered eligible for the present study. For the purposes of the present research, only patients with a diagnosis of mild to moderate CTS, confirmed by neurophysiological tests,[15] with no indication for surgical treatment, were included. Patients were excluded if they presented one of the following: diagnosis of sensory and/or motor neuropathy other than CTS; previous surgery for CTS; treatment with ESWT, US, cryo-US or local injection of corticosteroid for CTS in the previous year; history of trauma to the wrist or arm; pregnancy.

The study protocol was approved by the local ethics committee. The experimental protocol was explained to the participants, specifying that wearing night orthoses or splints, as well as taking any medication used to control CTS symptoms, was not allowed during the study period, and their informed consent was obtained. Participants who satisfied the eligibility criteria were enrolled and then randomly assigned to group A (US), group B (cryo-US) or group C (ESWT) by a researcher not involved in the study using a random allocation sequence generated by a software. The group assignment was specified in to a sealed envelope that was opened 30 minutes before the intervention was due to start.

All the participants received a clinical evaluation before treatment started (T0), at the end of treatment (T1), and four weeks (T2) and 12 weeks (T3) after the end of the treatment (Figure 1).

All the data were analyzed by an independent assessor who was blinded to the randomization.

Every patient in all three groups received a complete clinical evaluation of pain, paresthesias and functionality of the hand.

To evaluate pain in the hand and wrist in the previous 24 hours, patients were asked to mark a point on a 10-cm visual analog scale (VAS), rated from 0 (no pain) to 10 (worst possible pain).

To evaluate the influence of paresthesias on actual symptomatology, patients marked a point on a 10-cm VAS, rated from 0 (no influence) to 10 (paresthesias are the predominant symptoms).

The Italian version of the self-administered Levine-Boston Questionnaire for CTS,[6, 16] the most commonly used outcome measure of assessment for improvements in clinical symptoms and functional recovery of patients with CTS, was used to further assess pain and functionality of the hand. Briefly, it is divided into two parts. Part I (11 items) measures severity of hand symptoms, and part II (8 items) measures the functional status of the hand. Five answers to each question are possible and are scored 1-5 according to severity of the symptom or difficulty in a certain activity. Each score is calculated as the mean of the responses of the individual items. The higher the score is, the worse the symptom or function is.[16]

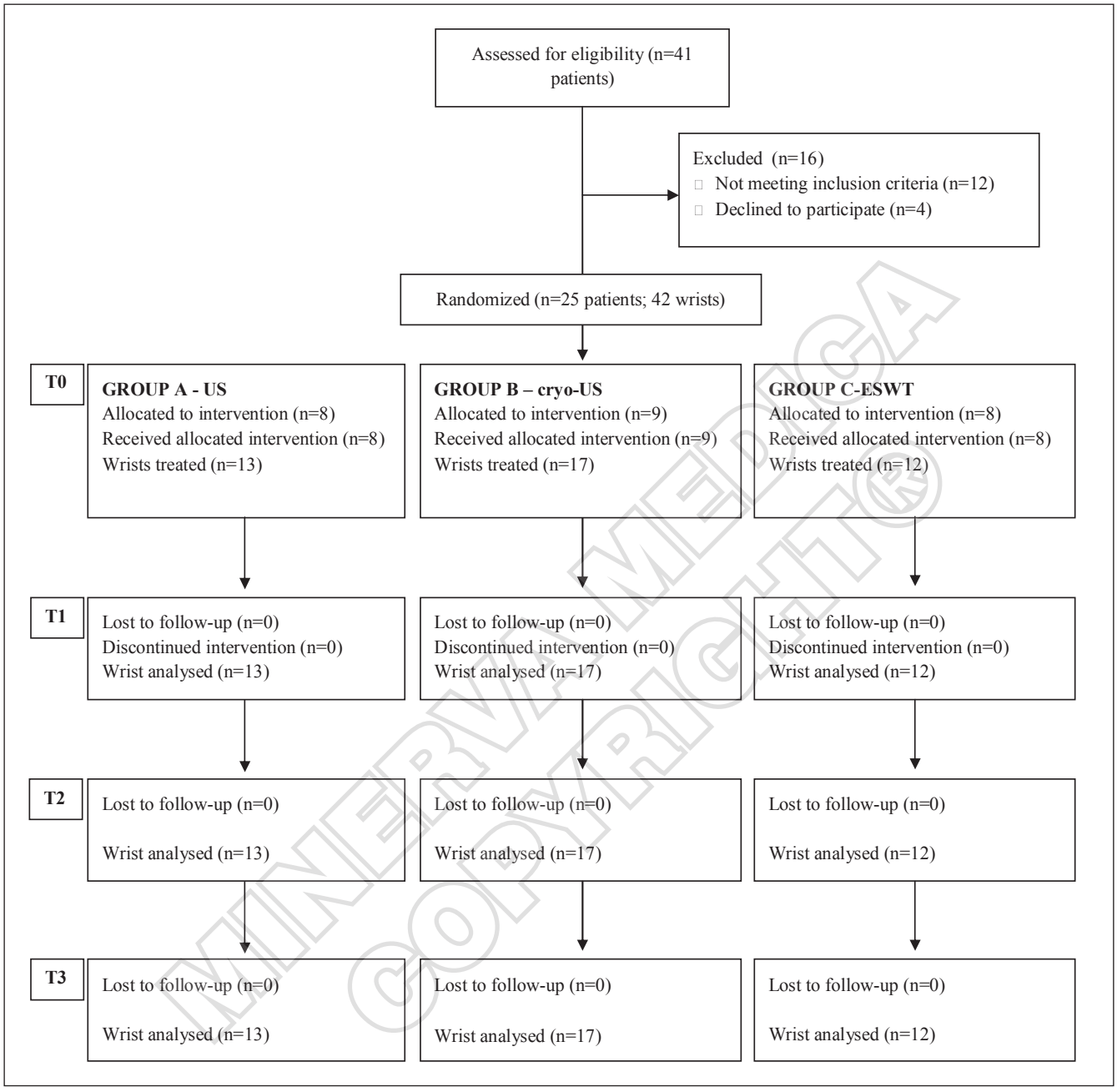

Figure 1.—Flow-chart diagram of the study. US: Ultrasound; ESWT: Extra-corporeal shock-wave therapy.

Patients in the US group received 15 sessions of US (5 sessions/week for three consecutive weeks) each lasting 15 minutes (frequency 1 MHz; intensity 1.0 W/cm² pulsed mode 1:4, with a transducer of 5 cm² and with aquasonic gel as couplant) on the palmar side of the wrist (FisioComputer USF-1, J&S, Rome, Italy).

Patients in the cryo-US group received 15 sessions of US (5 sessions/week for three consecutive weeks) each lasting 15 minutes (temperature of 0°C on the

skin; frequency 1 MHz; intensity 1.0 W/cm² pulsed mode 1:4, with a transducer of 5 cm² and with aquasonic gel as couplant) on the palmar side of the wrist (FisioComputer USF-1, J&S, Rome, Italy).

Patients in the ESWT group received 4 sessions over three consecutive weeks of low-intensity focused ESWT (2500 pulses, 0.05 mJ/mm²) (Modulith SLK system, Storz Medical, Tagerwilen, Switzerland) on the palmar side of the wrist.

All treatments in the three groups were performed by physicians (according to our national regulation shock-wave therapy must be administered by a physician and not by a physical therapist), who were different from those who performed randomization and from the assessor.

Sample size

The sample size, calculated by assuming a 2±3-cm pain difference between the pre- and post-treatment values on a 10-cm VAS, and a possible 20% withdrawal, indicated that 42 wrists would yield an alpha type I error of 0.01 and a beta type II error of 0.05.

Statistical analysis

The statistical analysis was performed using the MedCalc® 12.2.1.0 (MedCalc Software). Following randomization, normal distribution of all the variables analyzed was verified in both groups by means of a D'Agostino-Pearson test, and parametric or non-parametric tests were used, as appropriate. One-way analysis of variance (ANOVA) or Kruskal-Wallis were used, as appropriate, to determine baseline differences in demographic and clinical variables between groups.

A two-way ANOVA with treatment (US, cryo-US, ESWT) as between-group factor and time (T0-T1-T2-T3) as within-group factor was used to determine differences in VAS-pain, VAS-paresthesias and the Levine-Boston Questionnaire part I and part II between the three groups over time. A Tukey *post hoc* comparison was used to determine significant differences between the mean values when a significant main effect and interaction were found. All analyses were performed according to the intent-to-treat principle. The intent-to-treat analysis was carried out based on the last observation: patients who did not complete the treatment or did not undergo the post-treatment or follow-up assessments were assigned a poor outcome, corresponding to the last observation completed.[17] For all the analyses, the level of significance was set at $P<0.05$. A Bonferroni correction was applied to reduce type I error in interpreting the data.

Results

Forty-one patients were considered eligible for the study. After the inclusion and exclusion criteria were applied, 25 patients, and a total of 42 wrists, were enrolled and randomized to group A (8 patients, 13 wrists), group B (9 patients, 17 wrists) and group C (8 patients, 12 wrists) (Figure 1). No adverse events were recorded at any time during the study period, and all patients completed the assigned treatment and were analyzed at each follow-up (Figure 1). The demographic and clinical baseline characteristics of the three groups were well balanced (Table I).

The results of VAS for pain and paresthesias, as well as those of Levine-Boston questionnaire part I and part II for the three groups at each follow-up, are shown in Figure 2. At baseline, no differ-

TABLE I.—*Demographic and clinical characteristics of the three groups at baseline.*

	Group A (N.=13)	Group B (N.=17)	Group C (N.=12)	P
Age (years) (mean±SD)	56.5±9.4	54.7±9.2	59.1±12.5	0.53
Gender (F/M)	12/1	15/2	11/1	0.92
BMI (mean± SD)	28.7±4.7	27.7±6.6	26.5±2.6	0.57
Symptom duration (years) (mean± SD)	5.1±4.3	6.9±4.2	5.3±3.1	0.40
Paresthesias (yes/no)	13/0	16/1	11/1	0.60
Pain (yes/no)	8/5	11/6	8/4	0.97
Phalen test (positive/negative)	8/5	7/10	5/7	0.48
Tinel test (positive/negative)	8/5	6/11	2/10	0.07
Neurophysiological class (mild/ moderate)	4/9	10/7	7/5	0.25

F: females; M: males; BMI: body mass index

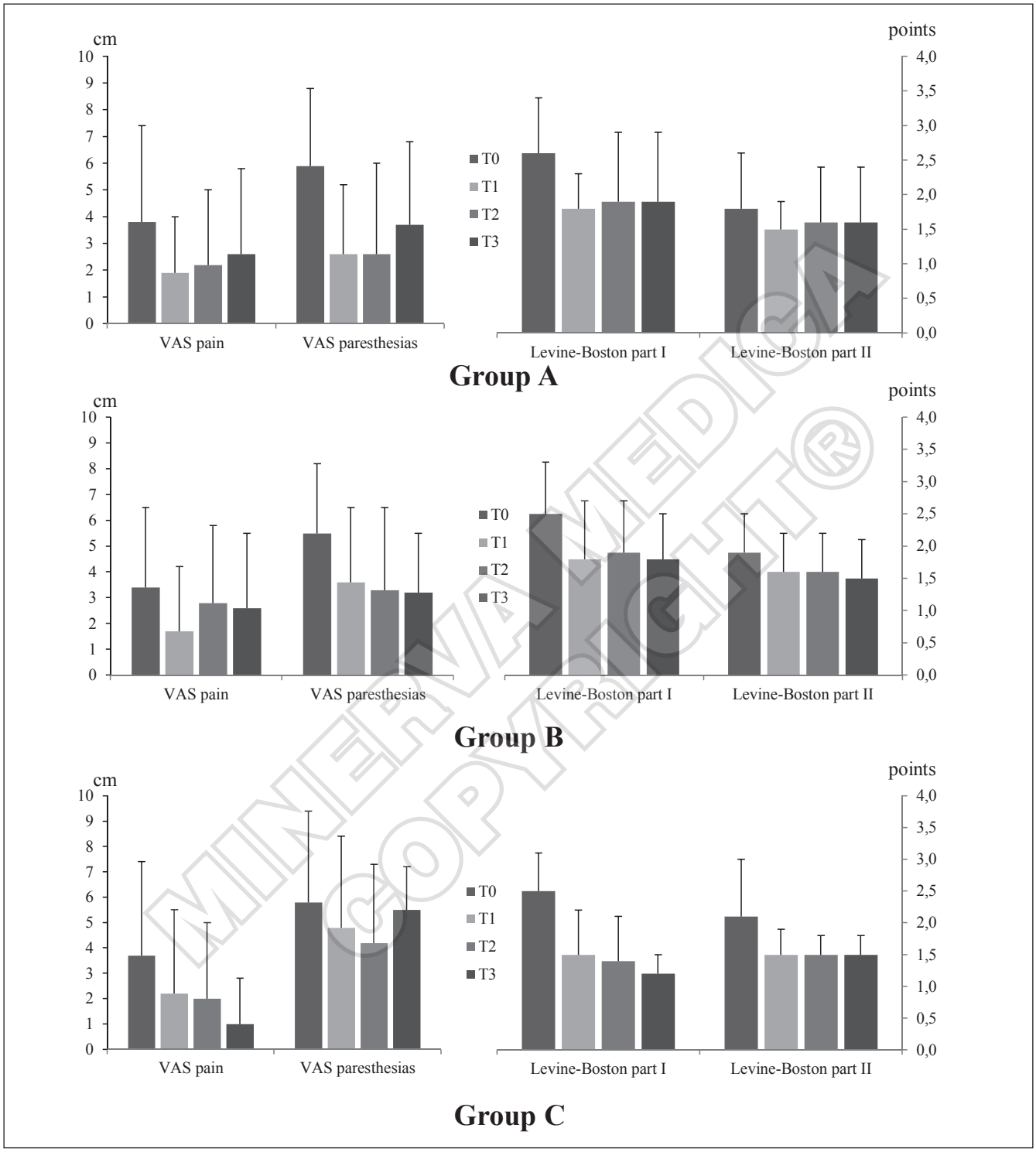

Figure 2.—Means (columns) and standard deviations (bars) of visual analog scale for pain (VAS pain) and for paresthesias (VAS paresthesias) and of Levine-Boston Questionnaire part I and part II in the three groups at each follow-up.

ences were detected between the three groups in pain ($F_{2,39}$=0.06;P=0.94), paresthesias ($F_{2,39}$=0.07; P=0.93), or the Levine-Boston questionnaire part I ($F_{2,39}$=0.09;P=0.91) and part II ($F_{2,39}$=0.67;P=0.52).

Two-way ANOVA revealed a significant effect of time (F_3=2.81; P<0.05), though not of treatment (F_2=0.33; P=0.72) or of the time*treatment interaction (F_6=0.48; P=0.82), for pain as measured by the VAS. No significant differences emerged from the *post hoc* analysis.

Two-way ANOVA revealed a significant effect of time (F_3=4.53; P<0.01), though not of treatment (F_2=2.66; P=0.07) or of the time*treatment interaction (F_6=0.53; P=0.79), for paresthesias as measured by the VAS. *Post hoc* analysis showed that paresthesias were significantly reduced at T1 (P<0.05) and T2 (P<0.01) when compared with T0.

The Levine-Boston questionnaire part I was significantly affected by time (F_3=11.91; P<0.001), treatment (F_2=3.95; P<0.05), though not by their interaction (F_6=0.42; P=0.86). *Post hoc* analysis demonstrated that the Levine-Boston questionnaire part I scores were significantly lower at each follow-up than at T0 (P<0.001). As regards treatment, patient scores in group C were better than those in either group A (P<0.05) or group B (P<0.05).

The Levine-Boston questionnaire part II was significantly affected by time (F_3=3.97; P<0.01), though not by treatment (F_2=0.035; P=0.97), nor by their interaction (F_6=0.44; P=0.85). *Post hoc* analysis demonstrated that the Levine-Boston questionnaire part II scores were significantly lower at T1 (P<0.05), T2 (P<0.05) and T3 (P<0.05) than at T0.

Discussion

The results of the present study show that, in the short-term period, *i.e.* up to 3 months after the end of treatment, patients affected by mild to moderate CTS might benefit from physical therapy treatments based on the application of US, cryo-US or ESWT.

All three groups displayed an improvement in pain from baseline, as measured by the VAS, with no between-group differences emerging from the *post hoc* analysis. However, the VAS, which was used to assess pain, only focused on generic pain in the hand and wrist in the 24 hours before testing. When the same characteristic was evaluated with an instrument specifically designed to measure symptoms in CTS (*i.e.* the Levine-Boston Questionnaire part I), we observed that pain relief in patients treated with ESWT was greater than in either of the other groups.

The efficacy of ESWT in improving symptoms in CTS is not a totally new finding. Recently, Seok *et al.*[14] demonstrated that a single session of ESWT was at least as effective as a corticosteroid injection in improving CTS-related symptoms, as measured by the Levine-Boston Questionnaire. The mechanism of action of ESWT on CTS has not yet been fully understood. A study by Monacelli *et al.*[18] showed that chronic compression of a nerve, as occurs in CTS, leads to an increased release of neuropeptides (including substance P, calcitonin gene-related peptide – CGRP) due to persistent neuronal depolarization, particularly from small nociceptor type C-fibers. It has been shown that the release of these two neuropeptides triggers vasodilation mediated by cyclic-GMP and by endothelial NO,[19] which in turn induces a self-perpetuating neurogenic inflammation.[20] Several studies have shown that low energy flux density levels (0.03 to 0.08 mJ/mm^2) of ESWT significantly reduce the number of cutaneous nerve fibers and the immune-reactivity to the CGRP, which may lead to denervation on a local scale and induce positive anti-nociceptive effects.[21] ESWT is also known to induce a short-term anti-inflammatory effect and a long-term tissue regeneration effect, both of which are mediated by nitric oxide (NO) induction.[22, 23] Unlike Seok *et al.*[14], we performed three ESWT sessions for two reasons: first, this therapeutic strategy allowed us to achieve more homogeneity in the overall duration of treatment in the three groups; second, as reported by Takahashi *et al.*[24], a second course of ESWT provides a cumulative effect on nerve fibers, with longer-lasting anti-nociceptive effects. Future studies are, however, warranted to determine the minimal dosage of EWST required in CTS to achieve long-lasting therapeutic efficacy.

Patients in our study receiving US or cryo-US also displayed a significant improvement in both pain and function after therapy. Ebenbichler *et al.*[8] demonstrated that US can improve symptoms as well as median nerve conduction velocity in patients with a neurapraxic grade of injury. In a rat model with a more severe injury, consisting of a partial crush lesion that produced both demyelination and axonal decay, Hong *et al.*[25] and Mourad *et al.*[26] demonstrated that ultrasound can accelerate the recovery of normal conduction velocity.

As for the underlying physical mechanisms, US interacts with tissue via local heating, cavitation, and/or radiation pressure. The study by Mourad *et al.*[26] suggested that radiation pressure, and not local heating or cavitation, is the main physical mechanism through which US accelerates peripheral nerve recovery. The fact that local heating does not represent the main therapeutic mechanism of action of US in CTS might explain why our patients who received cryo-US, which differs from US only insofar as the temperature at the skin is maintained at 0° C throughout the therapeutic session in cryo-US, displayed the same therapeutic benefit as those who received US.

Some studies also ascribe a prominent role in the regeneration of peripheral nerves to biological mechanisms, such as modulation of cytokines and neurotrophic factors, accelerated protein production, increased macrophage activity and angiogenesis.[27-29]

Interestingly, patients in all three groups in our study also displayed an improvement in hand function as measured by the Levine-Boston Questionnaire part II, which means that not only were symptoms reduced in patients, but the use of their hand in daily activities increased. This finding is particularly relevant to the type of patients we enrolled in this study, *i.e.* those with mild to moderate CTS, in whom non-operative treatment should be attempted before surgery is taken into consideration.[30]

It should be remarked that our results only refer to a 3-months follow-up period. In a chronic condition, like CTS, this short-term follow-up might not be satisfactory to assess if the proposed treatments are adequate to successfully and definitively manage the syndrome. Surgery remains the gold standard for CTS treatment,[5] with results reported in the literature indicating that symptoms in patients who undergo median nerve decompression disappear almost completely, even in the long-term. However, it has recently been demonstrated that CTS symptoms may improve without surgery,[31] which highlights the gaps in our knowledge of the natural history of this pathology.

Limitations

The main limitation of the present study is represented by the short-term follow-up. Owing to the chronic nature of CTS, longer follow-up periods are warranted in future studies to assess the long-term effects of ESWT and US on this pathology.

Another limitation of our study is that we did not assess neurophysiological changes after therapy. Other studies have, however, demonstrated that CTS patients do not, even when symptoms are relieved by treatment, display changes in neurophysiological parameters.[6, 14] One possible explanation is that symptoms are maintained by small fibers, rather than by modified myelinated fibers.[32, 33] Moreover, the subjective assessment of CTS symptoms is considered increasingly important, and even more so than EMG results, when decisions on the need for treatment, including revision surgery, need to be taken.[34]

Conclusions

Patients with mild-to-moderate CTS might benefit in the short term period from the application of US, cryo-US or ESWT. According to our results all these modalities have led 3 months after therapy ended to a subjective improvement of both pain and function. Due to the chronic nature of CTS, future studies with longer follow-ups are needed to clarify the long-term efficacy of physical modalities in CTS.

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