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● *Original Contribution*

SHOCKWAVE THERAPY IN THE MANAGEMENT OF COMPLEX REGIONAL PAIN SYNDROME IN MEDIAL FEMORAL CONDYLE OF THE KNEE

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Abstract—The aim of this prospective study was to assess the efficacy of shockwave (SW) therapy in the management of complex regional pain syndrome (CRPS). In this study, 30 patients (pts) who were affected by CRPS of the medial femoral condyle and unresponsive to previous standard physiotherapeutic and pharmacological treatment underwent 3 SW sessions at 72-h intervals, each consisting of 4000 shocks emitted by a MiniLith SL1 Storz electromagnetic generator. An energy flux density (EFD) of 0.035 or 0.09 mJ/mm^2 was used, depending on how well the patient endured the pain during the treatment. Satisfactory results were observed in 76.7% of the cases (23 pts) at the 2-month follow-up (FU) visit, and in 80% (24 pts) at the 6-month FU visit. The therapeutic effects of SW were caused by decreasing pain. The significant improvements we obtained bear witness to the potential value of SW therapy in the management of CRPS. (E-mail: angelanotarnicola@yahoo.it) © **2010 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Complex regional pain syndrome, Shockwave therapy, Knee.**

INTRODUCTION

Complex regional pain syndrome (CRPS) can develop after trauma and is particularly frequent in the extremities. Two types of CRPS can be distinguished: type I is characterized by a dysfunction of the autonomic and motor nervous system and is associated with sensory symptoms such as spontaneous pain, allodynia and hyperalgesia, whereas type II is generally secondary to a nerve lesion (Marinus and Van Hilten 2006). It has been suggested that the onset and persistence of CRPS could also be attributable to the release of reactive oxygen products, neuropeptides and inflammatory mediators (CKs) associated with sensitization of the local nociceptive fibers (Huygen et al. 2002). This phenomenon induces capillary vasospasm both at the arterial level, causing a reduced flow of nutrients to the bone substance and localized osteoporosis, and at the venous level, resulting in severe edema of the soft tissues (Birklein 2005).

Current treatment regimens largely rely on drugs that modulate the neuropathic pain (antiepileptics, tricyclic antidepressants or opioids) or cause bone recalcification (bisphosphonates); such drugs are used in combination with physiotherapy (magnetotherapy, functional rehabilitation or lymph drainage). The use of nerve blockades, spinal pumps, bone marrow and peripheral nerve stimulators is controversial (Hsu 2009).

To the best of our knowledge, the efficacy of shockwave (SW) therapy to treat patients affected by CRPS type I has not previously been discussed and evaluated. The rationale for the application of SW therapy in this type of disease is based on clinical and experimental studies that have demonstrated the efficacy of this procedure in managing neuropathic pain (Brown et al. 2005).

MATERIALS AND METHODS

Between January 2005 and December 2008, 30 patients (15 male, 15 female) aged between 25 and 65 years (49.7 ± 9.8) affected by CRPS type I of the medial

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femoral condyle (MFC) and admitted to the Outpatients Clinic of the Orthopedics Department of Bari University Hospital (Italy) were enrolled in this study after giving written informed consent. This prospective clinical study was approved by the Local Ethics Committee. The study observed the Declaration of Helsinki ethical principles for medical research involving human subjects.

Inclusion criteria were:

1. Diagnosis of CRPS type I according to the IASP criteria (Stanton-Hicks et al. 1995).
2. Localization of the disease in the MFC.
3. Clinical history lasting at least six months and refractory to previous classic treatment (physiotherapeutic and pharmacological) for at least three months.
4. Spontaneous pain scoring 5 or more on the visual analogue scale (VAS) scale.
5. Age ranging between 18 and 70 years.

Exclusion criteria were:

1. Presence of CRPS type I in other sites.
2. Presence of other diseases of the affected knee (meniscopathy, ligament lesions, osteoarthrosis or fracture).
3. Contraindications to SW treatment (infection or cancer of the area, carriers of a pacemaker or defibrillation device, pregnancy or epilepsy).

CRPS type I was diagnosed by magnetic resonance imaging (MRI) in the left knee in 10 patients and in the right knee in 20 patients at least six months before entering the study. A randomized design with a placebo-control group was not feasible for ethical reasons, as pointed out in many previous works (Breuer et al. 2008; Kiefer et al. 2008).

All patients underwent assessment before the treatment and during follow-up (FU) visits after two and six months using the VAS scale and the Knee Society Score (Insall et al. 1989) and by performing MRI of the affected knee.

Extracorporeal shockwaves were administered using an electromagnetic generator, the Minilith SL1 (Storz Medical AG, Kreuzlingen, Switzerland). The protocol established three sessions, at 72-h intervals; in each session 4000 shocks were administered, in accordance with the treatment indications for bone disease, and the energy flux density (EFD) was set at 0.035 mJ/mm^2 (medium-low EFD) or 0.09 mJ/mm^2 (medium-high EFD), depending on the patient's degree of pain tolerance. Although some patients suffered a certain amount of pain, none required an anesthetic and no treatment side-effects were observed.

At the end of the treatment, each patient was given a knee guard with lateral padding that left the rotula free, and all types of physical or sports activities were suspended for 60 d. According to the Knee Society Score (Asif et al. 2005), the clinical results were classified as: excellent (80 to 100), good (70 to 79), modest (60 to 69) or poor (<60), where the first two classes were regarded as satisfactory and the last two as unsatisfactory.

Statistical analysis

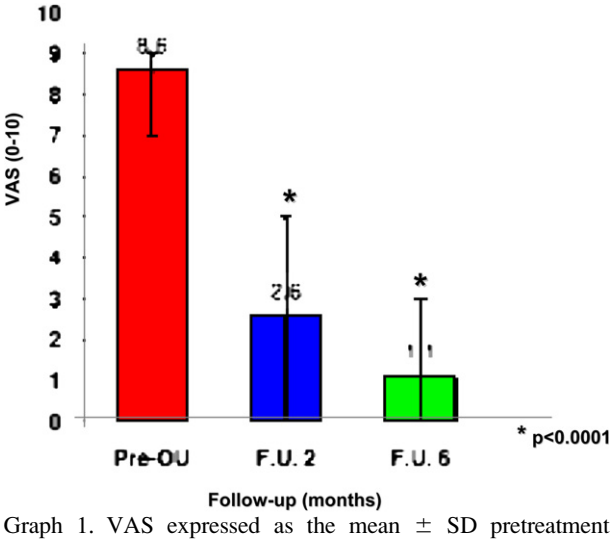
Continuous variables were expressed as the mean, including standard deviation and range, and categorical variables were expressed by a frequency distribution, including the 95% confidence intervals of the proportions. The analysis of variance test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. A p-value of < 0.05 was considered significant.

Data processing was performed using Epi-Info 6.00 software (public domain software, Centers for Disease Control and Prevention, Atlanta, GA, USA; World Health Organization, Geneva, Switzerland).

RESULTS

Medium-low EFD (0.035 mJ/mm2) was administered to 14 patients (46.7%; 95% CI = 28.8–64.5) and medium-high EFD (0.09 mJ/mm2) was administered to the other 16 (53.3%; 95% CI=35.5–71.2) because of their greater tolerance for pain (Table 1).

A significant difference was observed at the two- and six-month FU visits in both the medium-low EFD (chi-square = 43.3, $p < 0.001$) and medium-high EFD groups (chi-square = 40.6, $p < 0.001$) (Table 1). The VAS score dropped from the pretreatment value of 8.6 (±0.9) (range 7 to 10) to 2.6 (±1.3) (range 0 to 5) at the 2-month FU and to 1.1 (±1.2) (range 0 to 3) at the 6-month FU (F = 364.9; $p < 0.0001$) (Table 1, Graph 1).



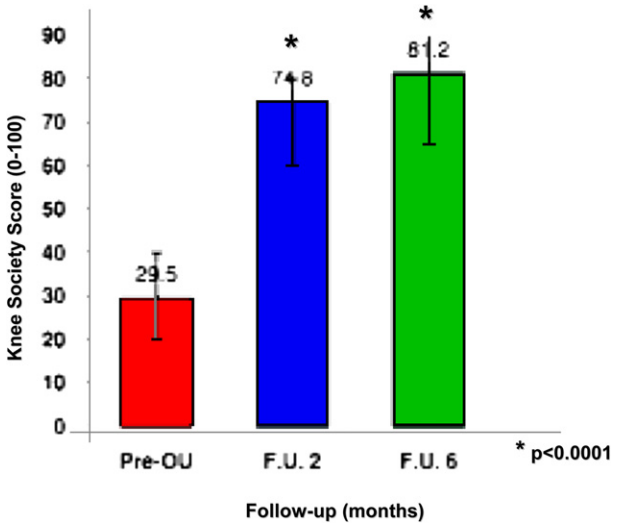
Graph 1. VAS expressed as the mean ± SD pretreatment (Pre-SW) and at the two-month (FU2) and six-month (FU6) follow-up visits.

The Knee Society Score (KSS) showed a significant functional recovery, rising from the pretreatment value of 29.5 (±7) (range 20 to 40), which was classified as poor, to

Table 1. Patients' (pt) data (age, sex) according to the EFD of the SW protocol and the clinical (VAS) and functional (KSS) results expressed as the mean ± SD pretreatment (Pre-SW) and at the two-month (FU2) and six-month (FU6) FU visits

Pt	Age (y)	Site	Sex	Energy (mJ/mm^2)	VAS (>5) pre-SW	VAS FU2	VAS FU6	KSS pre-SW	KSS FU2	KSS FU6
1	50	Right	M	0.035	8	3	0	25	80	90
2	53	Right	M	0.035	9	2	0	20	85	95
3	45	Right	M	0.035	10	1	0	35	70	80
4	56	Right	F	0.035	8	1	0	40	75	85
5	38	Left	F	0.09	9	4	3	20	60	65
6	43	Right	M	0.09	9	3	2	35	70	80
7	60	Left	F	0.09	8	2	0	35	85	90
8	47	Right	F	0.09	7	1	0	20	80	80
9	54	Right	F	0.035	9	3	0	35	75	75
10	65	Left	M	0.09	8	3	1	25	80	85
11	25	Left	F	0.035	10	5	3	20	65	65
12	55	Right	F	0.09	8	3	0	30	85	90
13	48	Right	M	0.09	8	0	0	25	80	85
14	57	Left	F	0.09	7	1	1	40	90	90
15	54	Left	M	0.035	9	1	0	25	80	85
16	65	Right	M	0.09	7	2	0	35	75	80
17	60	Left	M	0.09	8	3	3	35	80	85
18	53	Right	F	0.035	8	4	2	30	70	80
19	50	Right	F	0.09	8	2	1	35	70	80
20	40	left	M	0.035	9	2	1	30	75	85
21	38	Right	M	0.035	10	5	3	20	65	65
22	53	Right	M	0.035	10	4	3	25	60	65
23	50	Right	F	0.09	9	4	3	20	65	65
24	54	Left	F	0.09	8	2	1	25	75	85
25	42	Right	M	0.09	9	3	1	40	85	95
26	25	Left	M	0.035	9	4	2	25	65	75
27	51	Right	F	0.035	8	3	1	35	80	85
28	43	Right	F	0.035	9	1	0	35	70	95
29	56	Right	M	0.09	10	3	2	25	65	65
30	60	Right	F	0.09	8	2	0	40	85	90
Mean	49.7			2.6	8.6	2.6	1.1	29.5	74.8	81.2
SD	9.8			1	0.9	1.3	1.2	7	8.2	9.7

74.8 (±8.2) (range 65 to 90), classified as good, at the 2-month FU and 81.2 (±0.4) (range 65 to 95), classified as excellent, at the six-month FU ($F = 344.2$; $p < 0.0001$) (Table 1, Graph 2).



Graph 2. Knee Society Score expressed as the mean ± SD pretreatment (Pre-SW) and at the two-month (FU2) and six-month (FU6) follow-up visits.

Analysis of the mean differences between the VAS and KSS values per treatment type (medium-high or medium-low EFD) did not reveal significant differences between the two groups ($p > 0.05$). At the six-month FU, the mean VAS score was 1.1 (±1.1) (range 0 to 3) in subjects treated with medium-high EFD *versus* 1.1 (±1.3) (range 0 to 3) ($t = 0.5$; $p > 0.05$) in those treated with medium-low EFD. No difference was found in the mean value of KSS after medium-high EFD (81.9 ± 9.5) (range 65 to 95) or medium-low EFD (80.4 ± 9.9) (range 65 to 96) ($t = 0.5$; $p > 0.05$).

Before SW treatment, the MRI sequences of all of the study patients showed hypo-intense signals in T1-weighted imaging and hyper-intense signals in T2-weighted imaging in the bone marrow, joints, soft tissue and skin at the medial condyle of the knee. Fibrosis and inflammatory infiltrates were also frequently present. These MRI findings suggest the presence of hemodynamic abnormalities caused by sympathetic abnormalities, microangiopathy or both, which may lead to ischemia and interstitial edema of affected tissues (Nishida et al. 2009). None of our patients showed a regression of these MRI pathology signs during the previous months before SW treatment.

After treatment, MRI demonstrated that no signs of pathology were present in 21 patients (70%; 95% CI = 48.4–91.6) after two months and in 25 patients (83.3%; 95% CI = 70–96.7) after six months; an improvement in the pathology signs was seen in six patients (20%; 95% CI = 5.7–31.3) at the two-month FU (Figs. 1–3) and in five patients (16.6%) at the six-month FU. Persistence of the pathology signs only occurred in one patient (3.3%; 95% CI = –3–9.8) at the two-month FU (chi-square = 83.1; $p < 0.0001$). None of the patients became worse after treatment.

In conclusion, we obtained satisfactory results in 76.7% of the cases (23 patients; 95% CI = 61.5–91.8) at the two-month FU and in 80% of the cases (24 patients; 95% CI = 65.7–94.3) at six-month FU.

DISCUSSION

Extracorporeal shockwaves are defined as a sequence of single sound impulses characterized by a high-pressure peak (100 MPa) and pressure rise (<10 ns) and a short duration (10 μs). Produced by an appropriate generator, they are focused on a specific area, with an EFD ranging from 0.03–0.11 mJ/mm^2 (Gerdesmeyer et al. 2002). SW therapy was first used in a patient in 1980 to disintegrate kidney stones (Chaussy et al. 1980), but in the last 20 years it has been successfully used to treat a variety of orthopedic diseases such as pseudoarthrosis, tendinopathy (both calcific and noncalcific) and muscle trauma (Wang et al. 2001). Studies and reports in the literature have described a short-term anti-inflammatory effect and a long-term tissue regeneration effect, both of which are mediated by nitric oxide (NO) induction (Mariotto et al. 2005).

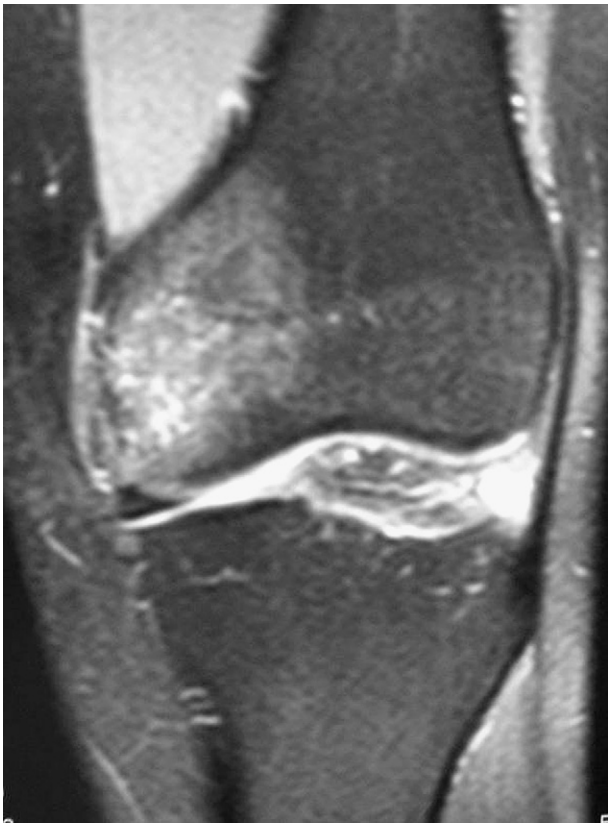


Fig. 1. MRI showing intraspongious edema of the internal femoral condyle of the knee in a patient of this study before SW treatment.

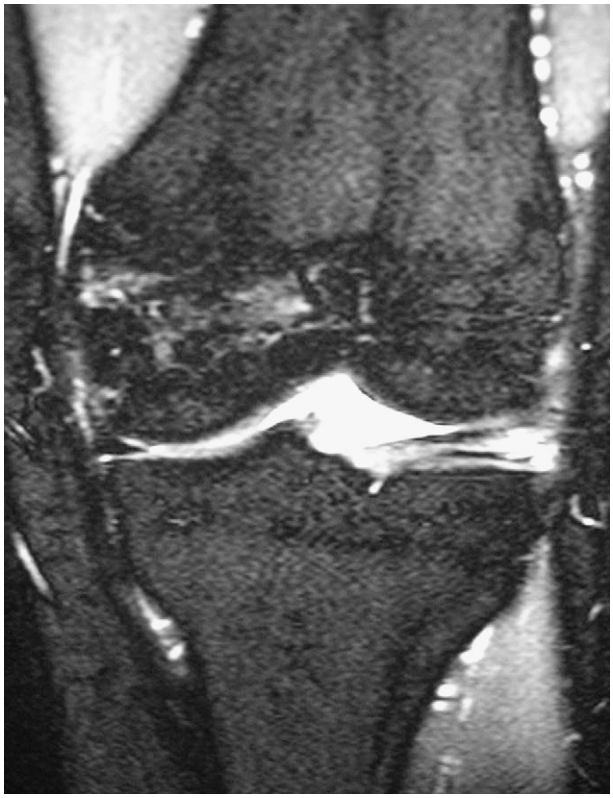


Fig. 2. MRI showing a reduction of the intraspongious edema in the patient from Fig. 1 at the two-month follow-up visit.

The rationale for the use of SW therapy to treat CRPS type I is principally based on the possibility of modulating the pain generated by the sympathetic nervous system. In fact, this disease is triggered by pain after trauma, which leads to capillary vasospasm, causing edema of the spongious bone caused by the lymph stasis and localized osteopenia that results from the reduced blood flow (Birklein 2005). It is recognized that SW treatment is able to bring about immediate pain relief because of desensitization of the local nociceptive fibers and the release of substance P (Bolt et al. 2004; Ohtori et al. 2001); the early clinical efficacy in the treatment of osteonecrosis of the head of the femur is largely dependent on this effect (Alves et al. 2009).

We applied medium-low and medium-high EFD without statistically significant differences in the results.

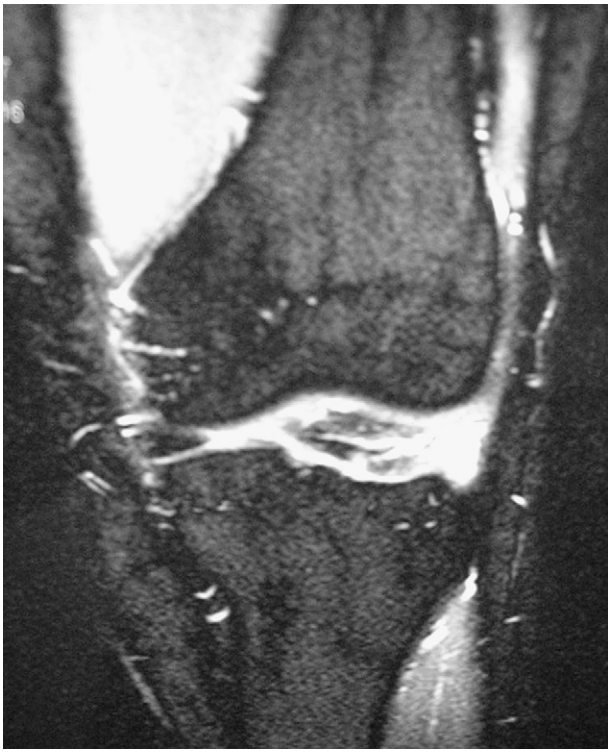


Fig. 3. MRI showing complete resolution of the intraspongious edema in the patient from Figs. 1 and 2 at the six-month follow-up visit.

Indeed, it is demonstrated in the literature that various energy levels cause nerve fiber stimulation (Rompe et al, 1998; Takahashi et al, 2006), but a higher intensity should obtain the greatest and most prolonged effects (Wu et al. 2008). We suggest the use the higher energy level used in our study. It may be interesting to verify the effects using a higher EFD.

SW treatment has been shown to promote neoangiogenesis (Stojadinovic et al. 2008), to have anti-inflammatory and anti-edemagenic properties (Mariotto et al. 2005), to have a collagen synthesis action (Christ et al. 2008), to induce an osteogenetic stimulus (Tamma et al. 2009) and to recruit stem cells by chemotaxis to differentiate along specific lines (Hofmann et al. 2008; Chen et al. 2004). Therefore, the application of a second course of SW could not only provide a cumulative effect on nerve fibers, with a longer-lasting antinociceptive effect (Takahashi et al, 2006), but could also act on the remaining alterations of ischemia and osteopenia in the damaged tissues, breaking the vicious circle of pain-ischemia-osteopenia of CRPS type I.

Nonfocused and more recently defocused SWs are emerging for the treatment of superficial skin and connective pathologies (Angehrn et al. 2007). Bolt et al. (2004) reported that in horses these nonfocused shockwaves are able to contribute to post-treatment analgesia, decreasing the sensory nerve conduction velocities in superficial nerves. Further studies should investigate their efficacy in the treatment of CRPS type I, in consideration of the deeper tissues being treated.

The results of this study suggest that extracorporeal SW treatment is effective in treating CRPS type I, mainly through the modulation of pain. This effect is obtained by applying three sessions of 4000 impulses at middle EFD using a focalized device. The data also suggest that improvements from the treatment may have a latent period lasting from 2–6 months.

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