reports

Case Report

Diamagnetic Therapy in a Patient with Complex Regional Pain Syndrome Type I and Multiple Drug Intolerance: A Case Report

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Abstract: Complex regional pain syndrome (CRPS) is a neurologic chronic pain condition hard to diagnose and treat, and able to significantly impact the quality of life. Currently, the available multimodal, individualized treatments (i.e., pharmacological and non-pharmacological therapies including invasive procedures) are aimed only at symptom control. Herein, we report a 69-year-old Caucasian female who came to our attention due to a 3-year history of severe (10/10) burning pain in her right ankle, along with oedema and local changes in skin color and temperature, which occurred after the ankle sprain. Previous pharmacological attempts failed due to multiple drug intolerance. Clinical examination confirmed the CRPS type I diagnosis, and a weekly diamagnetic therapy protocol was started since the patient refused further medications and interventional procedures. After 10 weeks of treatment, a significant ($p < 0.01$) reduction in pain severity and absence of oedema (difference in ankles' circumference: from 3 cm to 0) were observed, with consequent improvements in quality of life and no adverse events. Although high-quality clinical evidence is still lacking, our case report suggests further investigating the potential use of diamagnetic therapy as a non-invasive and safe adjunctive treatment for CRPS, and as an alternative when patients did not benefit from drugs and/or refuse invasive procedures.

Keywords: algodystrophy; CRPS; drug intolerance; magnetic fields; PEMFs; physical therapy

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1. Introduction

Complex regional pain syndrome (CRPS) is a painful chronic neurologic condition that can deeply impact quality of life, both functionally and psychologically [1]. CRPS typically develops in a distal extremity after acute injury (mainly trauma and surgery), although a small but not a negligible percentage of patients (up to 10%) may have no inciting events [2]. CRPS is confined to a body region and characterized by continuing pain that has no dermatomal distribution and is disproportionate to any inciting event, together with sensory (hyperalgesia and/or allodynia) vasomotor, sudomotor, motor/trophic signs and symptoms [3,4]. Based on the absence or presence of a specific nerve lesion, it can be classified into two different subtypes: CRPS I and CRPS II, respectively [1]. Despite advances in understanding, the pathophysiologic mechanism associated with its development has not been fully clarified yet. CRPS seems to be the result of a multifactorial

interplay between maladaptive pro-inflammatory response, autonomic dysfunction, altered somatosensory representation in the brain, and increased peripheral and central sensitization [4]. Furthermore, CRPS progression might be affected by genetic predisposition and psychological factors [1].

The treatment of CRPS is aimed at symptom control, and for each patient, it is established considering the severity, duration, and the functional and psychological impact of the symptoms. A multidisciplinary approach combining physical/occupational/psychological therapies, pharmacological treatments (i.e., neuropathic pain medications, non-steroidal anti-inflammatory drugs, bisphosphonates), and interventional procedures (i.e., sympathetic nerve block, spinal cord stimulation, dorsal root ganglion stimulation) is highly recommended [1,2].

Among bio-physical therapies, a progressive extension of the potential applications of the pulsed electromagnetic fields (PEMFs) has been observed over time, which has included wound healing and an increasing number of muscle-skeletal disorders [5]. PEMFs seem to be a promising stand-alone or adjunctive treatment for many muscle-skeletal diseases, due to their non-invasiveness, safety, and efficacy [6]. From a physics standpoint, PEMFs are nonionizing, nonthermal, low-frequency dynamic fields with specific waveforms and amplitudes, produced through pulsing current [7,8]. Their efficacy (especially at frequencies < 100 Hz) in inflammatory disorders, as well as in relieving pain and improving motor function has been widely demonstrated [9]. Nevertheless, the exact mechanism by which PEMFs exert their effects at the cellular and molecular levels has yet to be clarified [6] and various hypotheses have been proposed. High-intensity, low-frequency PEMFs seem to be able to affect the ion balance and membrane exchanges at the cellular level, and also propagate their effects through the signal transduction pathways [10], impacting cellular functions (e.g., differentiation, proliferation, interaction with extracellular matrix and other cells) [11].

Furthermore, they move water, ions and molecules and allow the exploitation of the water repulsive effect of diamagnetism on biological tissues [12]; for this reason, the biophysical stimulation carried out with high-intensity, low-frequency PEMFs is also referred to as diamagnetic therapy [13,14].

Herein, we present a 69-year-old Caucasian female suffering from CRPS for three years and multiple drug intolerances, successfully treated with diamagnetic therapy.

2. Case Presentation

A 69-year-old Caucasian female patient (weight 65 kg, height 170 cm, BMI 22.49) came to our attention due to a 3-year history of severe burning pain in her right ankle along with oedema and alternating periods of color changes (reddish or bluish) and/or temperature. Since the onset of these symptoms, which occurred after an ankle sprain, she reported being limited in work and activities of daily living. The severity of her pain was 10/10 on a numeric rating scale (NRS), with an impossibility to tolerate any mechanical stimulation, including sensory stimulation from clothing or blankets. She also reported impaired sleep, mainly difficulties in falling asleep.

The patient had a history of arterial blood hypertension (treated with bisoprolol 1.25 mg OD and valsartan 80 mg OD), cervical and dorsal spondylosis, arthrosis in genu varum (treated with intra-articular hyaluronic acid injection), bilateral hallux valgus and calcaneal spurs.

A diagnosis of CRPS type I was performed two years ago. She was treated with a large number of anti-inflammatory drugs (both steroidal and non-steroidal), from which she had had a modest clinical benefit. However, the occurrence of not tolerated adverse events, mainly gastrointestinal, had led to the discontinuation of all the therapeutical attempts. Furthermore, a protocol with bisphosphonates (i.e., a once-day intravenous infusion of neridronate 100 mg every 3 days, 4 total infusions) has not been completed, due to a referred drug intolerance. Different efforts with physiotherapy (mainly with TECAR therapy), also failed to relieve pain and improve motor functioning.

Finally, an occasional treatment with acetaminophen (1000 mg as needed) was started, with scarce pain control (NRS: 10).

On observation, the patient walked with a limp. The right ankle showed an asymmetric color of the skin and peri-malleolar oedema that induced a difference in the ankles' circumference (3 cm major in the right respect to the left). Clinical examination revealed in the right ankle a deficit in strength, hyperalgesia, and allodynia without dermatomal distribution or differences in skin temperature or tropism. A specific nerve lesion was ruled out through the assessment of both physical examination and clinical documentation and using the Budapest criteria the diagnosis of CRPS subtype I was confirmed. The Italian validated version of the SF-36 questionnaire [15] quantified the impact of CRPS type I on the patient's quality of life, showing the lowest scores in bodily pain, physical functioning, and role limitations due to physical health and emotional problems.

Due to drug intolerance and hypersensitivity, the patient refused to start a pharmacological treatment. Therefore, bio-physical therapy was suggested, and a session of diamagnetic therapy was planned for ten weeks. During each weekly session lasting 25 min, the treatment was carried out with the patient in a sitting position. The diamagnetic pump (CTU MEGA 20®®-Periso SA. Pazzallo-Switzerland) was set to a combined protocol, partly pre-specified by the manufacturer and partly established by the clinician (see Table 1).

Table 1. Protocol applied during each treatment session.

Technical Specifications	Duration
Movement of liquids	
Intra L: 40-Extra H: 60	5 min
Endogenous biostimulation	
Slow fibres: Power 3	5 min
Joint	10 min
Pain control	
3 Hz	5 min

Magnetic flux density was 86 mT at the site of treatment.

Before each treatment, we assessed the pain intensity and the presence of tissues' oedema through the NRS score and the measurement of the ankles' circumference, respectively. The SF-36 questionnaire was re-administered at the end of the ten weeks of therapy.

We considered pain intensity, the difference in ankle circumference and SF-36 scores as measures of the treatment's efficacy. Finally, during each treatment session, we asked the patient if adverse events had occurred since we had established as measures of the treatment's safety the number and the kind of potential adverse events.

3. Results

At the end of the treatment session (week 10), we documented a significant ($p < 0.01$) reduction in pain severity (NRS: 2/10) and the absence of oedema, with an improvement in both qualities of life and sleep. Compared with baseline, higher scores on the SF-36 questionnaire were reported in bodily pain, physical functioning, and role limitations due to physical health and emotional problems. No adverse events were reported throughout the ten weeks of treatment (Table 2).

Table 2. Summary of the results.

Outcome		Outcome Measure	Baseline	Week 10
Efficacy	**Pain**	Numeric rating scale (0–10)	10/10	2/10
	Oedema	Difference in ankle circumference	3 cm	0
	Quality of life	SF-36 questionnaire	Physical functioning: 20% Role limitations due to physical health: 0% Role limitations due to emotional problems: 0% Energy/fatigue: 30% Emotional well-being: 40% Social functioning: 25% Pain: 10% General health: 30% Health change: 50%	Physical functioning: 60% Role limitations due to physical health: 50% Role limitations due to emotional problems: 66.7% Energy/fatigue: 50% Emotional well-being: 68% Social functioning: 50% Pain: 55% General health: 45% Health change: 100%
Safety	**Adverse events**	Number and type of adverse events	None	None

4. Discussion and Conclusions

In this case report, we describe the effect of diamagnetic therapy on CRPS in an elderly woman with multiple drug intolerance. Previous data [4] suggested that both female gender and extremity injury are risk factors for the development of CRPS. In this case, our patient has a history of injury, and this probably induced the development of this clinical condition. Despite the availability of different therapeutical approaches, a large number of patients have a poor outcome, experiencing some lasting symptoms, chronic pain, and disability [16], which negatively affect, in turn, the quality of life [17,18]. Due to the significant impact of the functional limitations associated with CRPS, patients suffering from this syndrome show lower scores in questionnaires assessing the quality of life, mainly in the physical domains, compared with patients with other chronic pain conditions [18]. In our patient, the negative impact of symptoms on quality of life was confirmed by low scores in bodily pain, physical functioning, and role limitations due to physical health and emotional problems. Regarding the impact on sleep quality, we excluded it from both the results table and discussions, since it was reported only as qualitative information, not quantified through a validated scale.

To date, little is known about the prognostic factors that might differentiate between patients with good or poor outcomes [16]. Since there is no successful "one-size-fits-all" approach and some of the therapeutic options are invasive techniques, new effective and non-invasive strategies are needed, particularly in patients who cannot benefit from pharmacological therapy (due to intolerance or ineffectiveness). In our case, establishing a non-pharmacological treatment was mandatory since (i) the patient presented multiple drug intolerance, a clinical entity often misdiagnosed and under-reported [19], because of which she was scared to start a new pharmacological therapy, and (ii) she refused to undergo interventional procedures, i.e., sympathetic nerve blocks. The failure of previous protocols of physiotherapy was also considered to establish a different type of therapy that could be of benefit to her.

The rationale for the use of PEMFs in muscle-skeletal disorders is based on findings suggesting that, among others, they might stimulate the production of the extracellular matrix and the differentiation of mesenchymal stem cells in osteoblasts [20–23].

The identification of new therapeutic targets for CRPS and the evaluation of their effectiveness is complicated by the lack of a full understanding of CRPS' pathogenesis, and by the obvious difficulties in comparing suffering patterns and pain severity between patients and animal models [24]. To provide evidence supporting the use of PEMFs in treating

CRPS, a recent literature review assessed the in vitro and in vivo studies on the effects of PEMFs on local osteoporosis and inflammation, currently the main therapeutic targets of CRPS [25]. PEMFs exert an anti-phlogistic effect mostly by increasing the expression of A2A and A3 adenosine receptors at chondrocytes, fibroblasts, and neurons level [26,27]. The anti-oedema action observed in our patient could be explained by preclinical data, which showed that PEMFs affect microcirculation, increasing microvascular perfusion [28,29]. When magnetic flux density is in the milli tesla ranges (86 mT in our case), there might also be effects on local immune pathologic response [9]. Moreover, PEMFs reduce the level of pro-inflammatory cytokines, including those involved in the rapid bone turnover and osteoporotic changes which occur during the chronic phase of the disease [30,31]. As regards the effects on osteoporosis, PEMFs promote osteoblasts' proliferation and differentiation, by activating soluble adenylyl cyclase, cyclic adenosine monophosphate (cAMP), protein kinase A, and cAMP response element-binding protein (CREB) signaling pathways [32,33]. On the other hand, they inhibit bone resorption through multiple mechanisms including the induction of osteoclasts apoptosis and the downregulation of nuclear factor κ B (RANK) and carbonic anhydrase II gene expression [34,35].

To date, there are no studies specifically aimed at evaluating PEMFs effectiveness as a single or combined treatment for CRPS type I. The only exception is a small sample size, randomized controlled trial (RCT) in which PEMFs were used in addition to calcitonin and stretching exercises, in patients who developed CRPS type I after a Colles fracture. Compared with the placebo group, no statistically significant differences were found in visual analogue scale scores of pain at rest and pain during activity, as well as in the range of motion [36]. This study was assessed in a Cochrane systematic review focusing on physiotherapy measures for CRPS, which concluded that there was low-quality evidence that PEMFs are not superior to placebo for the treatment of pain or range of motion in patients suffering from CRPS type I [37]. Although data was derived from an RCT, the evidence was downgraded to low quality since the trial was at high risk of bias [37]. Despite the lack of high-quality clinical evidence and findings supporting the rationale of the use of PEMFs only as an add-on to the pharmacological treatment of CRPS, our patient has benefitted from diamagnetic therapy as a single treatment [25]. Indeed, after the failure of previous non-pharmacological therapies and the impossibility to start other pharmacological attempts or interventional procedures, we observed the disappearance of oedema and the reduction in the severity of pain (NRS from 10 to 2) after the treatment protocol, with consequent improvements in quality of life and no adverse events. However, the limitations of our findings should be kept in mind, as they referred to a single patient experience. Historically, the observation of a single patient played a crucial role in generating hypotheses and suggesting new therapeutic options [38]. Case reports contributed to the recognition and description of new clinical entities, as also happened recently with the first cases of pneumonia reported in Wuhan in 2019 (which were then attributed to the novel coronavirus [39]), as well as to the detection of adverse/ beneficial drug side effects [40]. In this regard, there are, for example, the withdrawal from the market of some drugs (e.g., thalidomide, weight reduction agents, nonsteroidal anti-inflammatory drugs) and the discovery of new therapeutic applications for other ones (e.g., sildenafil, bupropion) [40]. Therefore, a single clinical observation has "high sensitivity for detecting novelty", and can improve the knowledge of the etiopathogenetic, clinical and therapeutic aspects of the diseases, especially of those considered rare [38,40]. On the other hand, it has "lesser specificity for medical decision making" [40], and validation with a larger cohort of patients with a long-term follow-up is mandatory. Another limitation is that PEMFs have well-documented dose-dependent effects [41], and should be considered when a treatment protocol is established. To date, standardized clinical protocols are not available and parameter selection in terms of frequency, intensity, and exposure time, is managed by the clinicians.

In conclusion, our case report suggests deepening the potential role of diamagnetic therapy as a non-invasive and safe adjunctive option for CRPS treatment. Moreover, it

might represent a useful alternative for patients who did not benefit from pharmacological therapy and/or refuse invasive procedures. There are in vitro and in vivo data suggesting the molecular mechanisms responsible for the effects of PEMFs on pain, inflammation, and osteoporotic alterations, supporting the rationale for their use in patients with CRPS, but high-quality clinical evidence is still lacking. Therefore, large-scale RCTs with long-term follow-up and treatment protocols with standardized parameters are needed to provide adequate evidence. Further investigations should be directed to a deeper understanding of the cellular and molecular effects of PEMFs, including potential adverse effects associated with long-term exposure.

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