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Evaluation of the Efficiency of the Magicramp® Device for Reducing Cramps Resulting from Oncological Treatments: "Double-Blind, Randomized Clinical Trial"

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Abstract

We identified that oncological treatments in general (chemotherapies, immunotherapies and radiotherapies) frequently cause peripheral neuropathy, including cramps, characterized by excess protons due to metabolic and neuronal factors, such as sudden changes in pH, uremia and aspects that affect neuromotor functions. Such situations and others like them are often neglected in treatment, which naturally concerns itself with the main problem: Cancer. Sometimes toxic solutions are implemented that have comorbid side effects, such as duloxetine (standard treatment). Based on monitoring of cancer patients who used the non-toxic product, called "Magicramp® Electrostatic Charge Reduction Cushion" (MECRC), approved in Europe more than 10 years ago, we carried out a controlled test in Brazil. In this clinical trial, we hypothesized that reducing excessive ionic charges (electrostatic charge), which is one of the side effects often described in the literature as "Chemotherapy-Induced Peripheral Neuropathy" (CIPN), would decrease or eliminate cramping, under the hypothesis that such elimination would prevent or attenuate muscular vulnerability to action impulses, and increase the power of relaxation through the same mechanism. In this double-blind and randomized clinical trial, 40 (forty) adult patients with muscle cramps caused by oncological treatments were tested, evaluating the degree of efficiency of the product that aims to reduce muscle cramps, by eliminating and/or reducing excess loads electrostatic ionic. Data from the clinical research conducted in this study are available online.

Keywords

Muscle Cramp, Action Potentials, Antineoplastic Combined Chemotherapy Protocols

1. Objectives

1) Investigate the effectiveness of grounding therapy for the treatment of nocturnal leg cramps in patients with chemotherapy-induced peripheral neuropathy (CIPN).

2) Evaluate the safety and tolerability of the "Magicramp® Electrostatic Charge Reducing Cushion" (MECRC) grounding mat in patients with CIPN.

3) Identify the mechanisms of action of grounding therapy in reducing cramps.

4) Provide scientific evidence to support the use of grounding therapy as a complementary treatment for CIPN.

5) Raise awareness about the potential benefits of grounding therapy for patients with CIPN and other health issues related to ionic imbalances and neuronal hyperexcitability.

2. Methodology

Patients undergoing cancer treatment and experiencing cramps were primarily recruited from the chemotherapy sector. This study was approved by both CONEP and ReBEC (WHO Primary Registry) [1]. They were briefed about the research, and upon their agreement and signing of ICF (Informed Consent Form), a pain and cramp questionnaire was administered. Subsequently, a placebo or control device was provided. Forty patients were randomly selected and allocated to form two groups of 20 individuals each. The Intervention Group (IG) used a pad with ion reduction technology, while the Control Group (CG) used a masked, blinded pad without ion reduction technology for cramp treatment. Patients were instructed to place the pad on their back for 15 minutes before bedtime and to leave it under the sheet at calf level, lower limbs, or a specific location experiencing cramps. Each patient underwent pain assessments (McGill pain scales) and a cramp questionnaire developed by the researchers. The McGill Pain Questionnaire is considered the best instrument for characterizing and distinguishing the affective, sensory, and evaluative components of pain, aiming to obtain qualitative and quantitative information from verbal descriptions. Patients were advised to use the pad with or without ion technology mainly after triggering treatments. After this period, participants were questioned via WhatsApp about the results. Patients who received placebo were given a Magicramp® technology pad as a gift at the end of the study.

3. Results

The study involved 40 participants using the Magicramp® MECRC cushion device, where 11 (27.5%) discontinued the research process, divided into four cat-

egories: 1) Loss of communication; 2) change in treatment; 3) treatment interruption; and 4) death. In addition to communication loss, for patients who dropped out due to a change in treatment, it was observed that changing the chemotherapy method reduced cramps, making the use of MECRC unnecessary. Of the patients who discontinued chemotherapy treatment, they were automatically no longer available to continue using the product, mainly due to withdrawal, claiming they no longer needed the product since they no longer suffered from cramps. There was a treatment discontinuation caused by the death of a 55-year-old female patient, with non-small cell lung cancer who had been treated with weekly monochemotherapy with CBP + PTX (Carboplatin AUC 2 + Paclitaxel), Cimetidine 300 mg/2ml Injectable, Dexamethasone 10 mg/2.5ml IV, Docetaxel: 75 mg/m^2 Ondansetron 8 mg/4ml IV, Gemcitabine 1 Gr Inj.). Of the remaining twenty-nine (29) participants, 13 were randomized to the treatment group (TG), and 16 were in the control group (CG); 11 individuals out of 13 who received the true cushion in the TG showed a true positive result (84%), demonstrating the product's efficacy in reducing cramps, while two (2) out of 13, or 16%, demonstrated the product's inefficacy. Fourteen (14) individuals in the CG, out of 16 who received placebo, had false-negative results, indicating the absence of the placebo effect in 87.5% of cases. Two (2) participants in the CG reported improvements, even though they received the placebo, resulting in a false-positive rate (12.5%), indicating, in these cases, the prevalence of partially hidden positive effects on the disease/symptom under research. The Predictive Value (PV) is the ability of a test or predictive model to correctly identify true positives and true negatives regarding a certain event or condition. The analysis of the Predictive Value of tests in patients who used MECRC revealed a PPV of 84.6% and an NPV of 12.5%. This indicates that 84.6% experienced a real reduction in cramps when using the product, while 12.5% did not observe this reduction when using MECRC. If we consider each modality, in those who used the

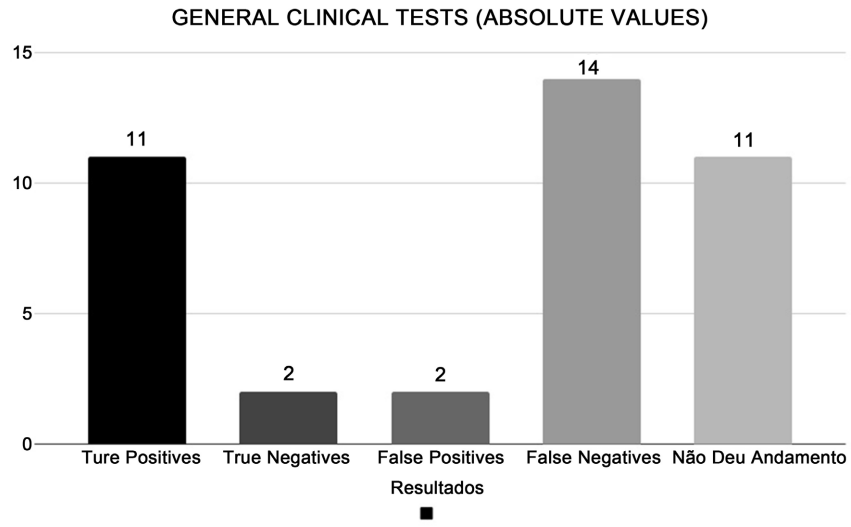

Figure 1. Absolute general values of clinical trials.

active ingredient device, 84% obtained a positive result, and in those who used placebo, only 12.5% obtained a positive result, that is, 87.5% obtained the expected negative result (Figure 1).

We did not obtain clear results regarding pain/medication distinction, attributed to the Hospital Araújo Jorge of ACCG in Goiás, Brazil, being rich in medicinal innovations, with numerous clinical trials employing new drugs. Additionally, patient records exhibited a wide variety of new oncological medications. Thus, for our small sample size, establishing causal relationships was unfeasible. Moreover, each participant reported various types of pain from the extensive McGill questionnaire, making it challenging to correlate specific types of pain with their respective medications among the 29 remaining patients with diverse interventions.

4. Conclusions and Importance

The efficiency of the MECRC product in the double-blind, randomized clinical trial was assessed based on the analysis of the Predictive Value (PV). The Positive Predictive Value (PPV) of 84.6% indicates that the majority of patients who used the product experienced a real reduction in cramps, confirming its effectiveness. However, the Negative Predictive Value (NPV) of 12.5% reveals the presence of false negatives and 16% of true negatives, indicating that the product may not be effective for all patients (Figure 2).

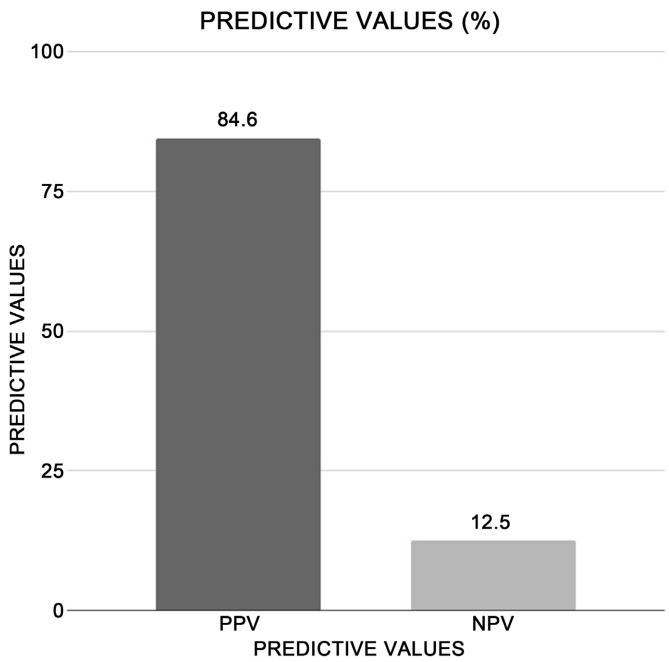

Figure 2. Predictive value percentages.

These results underscore the importance of considering individual variability in treatment response and emphasize the need for additional studies to identify factors influencing the effectiveness of MECRC. The analysis of the Predictive

Value provides valuable insights into the efficiency of a product in clinical trials and assists in making more informed clinical decisions.

The results suggest a partial efficacy of MECRC in reducing cramps, as evidenced by the true positives in the treatment group. However, the presence of false positives and true negatives may be explained by external or internal factors that could have interfered with the results. Not following the correct instructions for product use or a highly stressful and taxing environment for patients may have influenced questionnaire responses, leading to true negative results. Furthermore, regarding false positives, it is possible to consider the placebo effect or changes in medications throughout the treatment, which may modulate different reactions, increasing or decreasing cramps. Additional investigations with larger samples and robust clinical trials are needed to fully understand the therapeutic potential of MECRC in cramp treatment.

5. Margin of Error

Margin of error ≈ 0.1384 for a confidence interval of 1.96, *i.e.*, 95% confidence. P-value: 0.0001. Using Fisher's exact test:

The Fisher Exact Test Statistic value is 0.0001 (Table 1). The result is significant at $p < 0.05$.

Table 1. Easy Fishr exact test calculator.

Result	Treatment	Control	Marginal Row Totals
True Positive	11	2	13
False Positive	2	14	16
Marginal Row Totals	13	16	29 (Grand Total)

6. Efficiency by Modality

The efficiency of clinical trials in control and placebo patients is essential for evaluating the safety and efficacy of new medical treatments (Table 2). In trials with control patients, the treatment under study is administered and compared with other existing interventions or no treatment, while in placebo trials, one group receives the actual treatment and another receives an inactive substance. Effectiveness is measured by comparing results between groups, providing a direct assessment of treatment impact and its superiority over the placebo effect.

Table 2. Efficiency by modality.

Result	Numerical Proportion	Efficiency Percentage by Modality
True/Positive	11/13	0.84
True/Negative	2/13	0.16
False/Negative	14/16	0.88
False/Positive	2/16	0.13
Not Progressed	11/40	0.28

7. Structure of the Research Site (Araujo Jorge Hospital)

The Araújo Jorge Cancer Hospital served 945,082 patients through the SUS (Brazil's public health system), 61,399 through health insurance plans, and 25,273 privately. This totals 1,031,754 treatments in the 2021 annual report. The Oncology Unit of Anápolis attended to 89,785 (SUS), 3444 (health insurance plans), and 3930 (private), totaling 97,159 treatments. The overall ACCG total is 1,034,867 (91.7% SUS), 64,843 (5.7% health insurance plans), and 29,203 (2.6% private), summing up to 1,128,913 procedures in 2021. Such infrastructure and sample size provide the feasibility for numerous types of tests, resulting in a high confidence level in clinical trials, allowing for various types of trials such as comparative, double-blind, etc., thus achieving high performance feasibility in an academic-scientific environment. Additionally, team members already serve as clinical trial coordinators at https://www.accg.org/ and have good relations with their management, enabling us to conduct and complete phase 1 clinical trials and proceed to phases 2, 3, and 4.

8. Ethical Review Process

This study was conducted following the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of ACCG (Cancer Combat Association in Goiás) under approval number CONEP-CAAE: 65241622.4.0000.0031 and supported by the Institute of Teaching and Research with numbers 5,790,355 and 6,647,822. All participants provided written informed consent (ICF) before participating in the study; they received detailed explanations about the objectives, procedures, and potential risks involved. Informed consent was obtained in writing from all participants and registered in the Brazilian Clinical Trials Registry under number RBR-377gqvx. [1] The study protocol was submitted to the Research Ethics Committee on 03/07/2023, and approval was granted on 06/12/2022. Any recommendations or modifications requested by the committee were duly incorporated into the protocol before the study commenced.

9. Blinding

Placebo pads were randomized using 6-digit random numbers [2], where some numbers were placed as the experimental treatment of the device (true) and others referenced the placebo control group, where patients received pads without active principles. All placebo and control pads had a code hidden under the green label, and its meaning was revealed whether they were placebo or control at the end of the research, when pads with electrostatic discharge principles were donated to participants who received placebo. The researchers wrote down and entered the number on the back of the green label in the "Excel" spreadsheet. This number, both the researcher and the patient did not know whether it contained an active principle or a placebo until the end of the experiment.

10. Technology

The ionic charge reduction technology used is the technology developed and patented in Brazil, called Magicramp®, characterized by a small pad filled with antistatic material, used in the manufacture of antistatic plastics for industrial electronic applications. [3] [4] [5] [6] [7]

Composition of Magicramp®: A 100% cotton twill fabric; Antistatic material based on kaolin clay (a non-toxic mineral with anti-static properties) and bar soap. It is not magnetic, but only antistatic. It has no contraindication, even for pacemaker wearers. The duration of effectiveness of this material is 5 to 10 years. As a sanitary measure, the antistatic pads used for the study will be packed in a transparent plastic bag that does not compromise the antistatic properties.

11. Inclusion and Exclusion Criteria for Participants (Table 3)

Table 3. Inclusion and exclusion criteria.

Inclusion	Exclusion
Patients of both genders; with Chemotherapy-Induced Peripheral Neuropathy (CIPN); and or treatments that cause excess ions in the muscles and sudden changes in pH	Sciatic nerve related cramps; or previous history of cramps; or history of having mild and intermittent cramps, before the oncological approach.

12. Introduction

We observed that more aggressive radiotherapies and chemotherapies, by killing many cancer and normal cells, increase the concentration of proteins in the blood and kidneys, causing uremia and excess protons, facilitating the triggering of cramps, due to leaving the muscle contraction system closer and more vulnerable to exceeding the limit of the muscle action impulse, and also at the same time, preventing it from relaxing for the same reason. It was verified that chemotherapeutic agents containing platinum, taxanes, epothilones, vinca alkaloids, bortezomib, present "infusion reactions" (IRs) and chemotherapy-induced peripheral neuropathy (CIPN). Such side effects often require dose reduction or discontinuation of treatment. Even after the end of chemotherapy, radiotherapy and immunotherapy sessions, such adverse effects often persist and decrease the quality of life and survival after treatment, thus representing the increase in comorbidities, which may be mainly linked to the decrease in the quality of restful sleep, which is essential for good immune function, thus increasing unmodulated and generalized inflammation, pain, cytokine storm and other related effects. We reference works that highlight that such CIPN reactions occur in all patients who received high doses of chemotherapy. We observed that the electrochemical mechanism of cramps, as it is often related to the trapping and/or accumulation of ionic charges in the muscles, makes it easier to trigger the action impulse, by facilitating the surpassing of the action potential threshold, ge-

nerating with greater propensity and greater frequency, muscle contraction, accompanied by insufficiency of electrochemical mechanisms of muscle relaxation due to the excess of ionic present.

The known symptom of cramp was classified as a disease by the WHO—World Health Organization, through codes 67.2 (cramps due to heat) and 25.2 by ICD10 [8] (cramps and spasms) and with more relationships in ICD11 [9]. In DeCs (health descriptors) it has hierarchical number C10.597.613.500, being defined as: [10] [11]

> "Sustained spastic contraction of muscle fibers, usually painful. This may occur as an isolated phenomenon or as a manifestation of an underlying pathological process (examples: UREMIA, HYPOTHYROIDISM, MOTOR NEURON DISEASE, etc.). (Free translation from the original: Adams *et al.*, Principles of Neurology, 6th ed, p. 1398)"

Cramps are classified as both a disease and a symptom, and are admitted to be a symptom most of the time, neglected in medical care, especially in the context of cancer, which attracts more attention. Many medications and proposals have been made, but "the mechanisms are complex with alterations in ion channels (sodium, potassium and calcium), transient receptor potential (TRP) channels, mitochondrial dysfunction and immune cell interactions." [12] CIPN "occurs in ~20% of patients receiving standard doses of chemotherapy and in almost 100% of patients treated with high doses" [13] [14]

More recent research on the mechanism of cramps [15]-[22] reveals a diversity of relationships and causes [17] [23] [24] [25] [26] especially generated by chemotherapy [27] in lesions that occur in nerve fibers outside the central nervous system (peripheral neuropathy). In several relationships there is confirmation of the observation made by Luigi Galvani [28] [29] in the 18th century, where his tests identified an increase in the accumulation of ionic charges as the cause of the involuntary contraction that occurred in certain frogs. Currently, it is known that "in electromyography (EMG), involuntary muscle contraction is associated with repetitive firing of motor unit action potentials at high rates (up to 150 per second)" [30]. Similar reactions can also be seen in conditions resulting from chemotherapy-induced peripheral neuropathy (CIPN), where some chemotherapeutic drugs can cause [31]-[36] ionic cramps [37] [38] [39] [40] under "cramp discharge rates that are typically 150 Hz" [30] and/or "characterized electrically by repetitive firing of motor unit action potentials at rates of up to 150 per second."

One of the factors that stands out in different types of cramps is its high relationship with the neuronal-muscular trapping of electrostatic charge, in this third clinical trial of a series of several ongoing clinical tests on the evaluation of the efficiency of this method of reducing cramps, we tested a method of reducing ionic charges through Magicramp® pads [41] [42]. The idealizer of the clinical trial project and inventor of the pad containing grounding technology, Mr. Jean-Marc WILVERS, Belgian, reports that he started his studies motivated by

the strong childhood cramps [43] [44] (growing pains) that his own daughter felt, and that after failed attempts at a solution in several consultations with medical specialists in Europe, he decided to research for himself how to solve it. During his search, while visiting the Brussels library, he found the research of the old doctor Dr. Luigi Galvani (1737-1798), in which he identified the relationship of involuntary muscle contractions of a dissected frog in his laboratory, with the accumulation of ionic charges (electrostatic charges); [45] [46] Jean-Marc reports that reading Galvani's experiences reported in several works [28] [29] made him deduce a simple solution for his daughter, which would be the grounding of excess ionic charges and reduction of electrostatic charge in the muscles. He experimented and achieved success in a surprisingly simple way; then, he researched chemical elements that promote the reduction of ionic charges, as an alternative in the treatment of cramps, and observing the need mainly of people who live in large urban centers, without contact with the ground. [47] [48] [49] [50] [51], he noticed the frequency of nocturnal leg cramps that require grounding during sleep, during the metabolism producing excess protons, to then, with the demands involved, develop a grounding pad that has been used in Europe for over 10 years. [52]

Additionally, renal alterations are related to peripheral neuropathy and cramps [53], as urea—a product of hepatic protein degradation—accumulates in the blood due to difficulties in renal excretion, leading to uremia. This condition involves elevated plasma ions and nerve fiber damage. Chemotherapy is associated with a high cell death rate, which can result in intense protein release. This may increase the risk of uremia and peripheral neuropathy in cases of renal disease [54]-[60], and grounding methods have been seen to aid in the excretion of accumulated urea: "These results suggest that grounding during exercise inhibits hepatic protein catabolism or increases renal excretion of urea" [61].

While there are multiple causes of cramps that point to synergistic treatments [17], we focus here on decreasing ionic loads to elucidate the contribution of this technology, especially due to its rapid pain and cramp reduction outcomes. However, we emphasize the value of other methods and personalized cause studies, recommending actions that address the most significant root cause in each individual case, as the predominant cause may vary between different persons and scenarios.

In a prospective controlled clinical trial, neuromuscular electrical stimulation significantly reduced the frequency of skeletal muscle cramps, with a noted increase in the cramp threshold from 15.5 ± 8.5 Hz before intervention to 21.7 ± 12.4 Hz after intervention [62]. Similarly, satisfactory results were obtained in patients with back pain-induced cramps [40] [63].

A potential mechanism of ionic loads in cramps is highlighted below [13] [15] [16] [64]:

> "[...] the potential mechanism behind motor neuron hyperexcitability might involve the development of persistent inward currents in spinal motor neurons following contraction-mediated activation or sensory afferent sti-

mulation (1, 2, 20, 21, 26). The generation of persistent inward currents alters the relationship between synaptic input and motor neuron output, resulting in amplified and prolonged afferent inputs converging on motor neurons during cramp development." [...] "In conclusion, recent investigations suggest spinal involvement rather than peripheral excitation of motor neurons."

The etiology of cramps is disputed by two hypotheses in numerous studies [15]:

"One hypothesis attributes cramps to changes in motor neuron excitability (central origin), while another suggests they result from spontaneous discharges of motor nerves (peripheral origin)." [...] "These observations indicate that the action potentials observed during cramps are generated in the motor neuron soma, and that afferent synaptic inputs to motor neurons influence the development and termination of the cramp. However, these observations do not rule out the possibility of cramps being triggered exclusively in the periphery, with peripherally triggered cramps resembling common cramps. The study of contractions induced by peripheral nerve blockade has recently shed light on the relative peripheral and central roles in the origin and development of cramps."

A 2018 meta-analysis of 424 manuscripts highlights two prominent hypotheses focusing on two potential mechanisms: dehydration or electrolytic depletion mechanism, and the neuromuscular mechanism [16]. Electrolytic depletion and dehydration have been linked to chemotherapy [65] [66] [67], while a more recent study in 2022 suggests that the cause of cramps depends on various factors [68]:

"Cramp etiology varies based on the situation. It is not possible to pinpoint the causes; therefore, the focus should be on the physiological or pathological differences in which the cramp occurs, as different scenarios give rise to cramps. Muscle cramps associated with heat are often observed in sports, rigorous exercises, or physical activities, where significant loss of sweat and electrolytes are believed to be the underlying pathological mechanism."

The mechanisms of cramps are also described in relation to myosin [69]:

"Cramps can occur when muscles fail to relax properly due to myosin proteins not detaching from actin filaments. In skeletal muscle, ATP levels must be sufficient for myosin heads to bind and detach from actin, allowing for contraction or relaxation; inadequate ATP levels mean that myosin heads remain attached to actin. The muscle must recover (re-synthesize ATP) before myosin proteins can detach, allowing the muscle to relax. Skeletal muscles function as antagonist pairs, and the contraction of one muscle requires the relaxation of its opposing pair."

In general, it appears that any accumulation of ionic charge in the muscles

tends to make them rigid and can lead to severe cramps. This accumulation can stem from various causes, such as muscle development in children aged 3 to 8 years, orthopedic friction generated by a ventilator, exposure to vibrational environments, intense exercise and muscle friction, and ionic biochemical imbalances due to nutrient deficiencies or toxins, including chemotherapeutic agents [70] [71]. In such situations, the discharge or reduction of ionic charge is recommended as a good non-invasive approach to mitigate or manage the issue.

13. The High Toxicity of Certain Chemotherapies

Since the observation of reduced chemotherapy efficiency in 22 types of neoplasms in 2004, where the overall 5-year survival rate in adults was estimated to be 2.3% in Australia and 2.1% in the US [72], numerous studies have warned of its high toxicity, including the potential for hastening patient death [73] [74] [75]:

> "Drug toxicity may result in significant adverse effects, making it impossible for the patient's body to physically tolerate them. This would render the use of that specific medication impossible, as well as any medications that would exacerbate pre-existing clinical conditions. A patient's health may also deteriorate to the point where the use of certain medications becomes impossible during treatment, whether due to the medication itself or other factors."

Muscle cramps can be caused by various pathogenic mechanisms related to the disease: dehydration, electrolyte imbalance, vascular issues, anticancer drugs, as well as other medications (such as atorvastatin) and metabolic disorders. In a study evaluating 50 patients referred to a neuro-oncology unit for the onset of cramps, cancer-related toxicity or cancer treatment-related toxicity was identified as the cause in 84% of the patients [13] [42]:

> "Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent and dose-dependent complication of anticancer drugs, including platinum, taxanes, epothilones, vinca alkaloids, and newer agents such as bortezomib. It not only leads to dose reduction or discontinuation of treatment but also decreases the quality of life of cancer survivors. CIPN occurs in ~20% of patients receiving standard doses of chemotherapy and in nearly 100% of patients treated with high doses."

Chemotherapy brings various side effects, and the attack on cancer depends on there being no deviations of attack signals, generating an increase in cytokine storms [76] [77] [78], including Chemotherapy-Induced Peripheral Neuropathy (CIPN), which includes cramping among its symptoms.

14. Justifications

Potential side effects: Some treatments for CIPN (Chemotherapy-Induced Peripheral Neuropathy) may present undesired side effects. For instance, certain

medications may induce fatigue, nausea, vomiting, constipation, or other side effects that could be uncomfortable for patients.

Many health benefits are demonstrated by reconnecting to the earth [47], where an earthing pad can represent a reasonable solution for those who live almost exclusively in apartments.

> "Emerging scientific research has revealed a surprisingly positive and overlooked environmental factor in health: direct physical contact with the vast supply of electrons on the surface of the Earth. Modern lifestyle separates humans from this contact. Research suggests that this disconnection may be one of the major contributors to physiological dysfunction and malaise. Reconnection with Earth's electrons has been found to promote intriguing physiological changes and subjective reports of well-being. Earthing (or grounding) refers to the discovery of benefits - including better sleep and reduced pain - from walking barefoot outdoors or sitting, working, or sleeping indoors connected to conductive systems that transfer the Earth's electrons to the body. This article reviews earthing research and the potential of earthing as a simple, globally accessible modality of significant clinical importance."

Few efficient solutions are available for cramps in general, even though some results resolve one case or another [68].

> "So far, most medications used in the treatment of muscle cramps have low efficacy and even their therapeutic action is unreliable or unpredictable. What works in one person may not work in another. Regarding quinine, studies indicate that the drug may not be effective. And the drug is also associated with various disturbing adverse effects."

Alternative methods are justified for this essay for cramps caused by CIPN. According to these works, the only drug recommended by the "American Society of Clinical Oncology" was duloxetine, which is fraught with side effects with a synaptic signaling reduction action [12] [79].

> "No preventive therapy has shown significant clinical efficacy, although there are promising new agents such as histone deacetylase 6 (HDAC6) inhibitors, currently in early-stage clinical trials for cancer treatment. Drug repurposing, for example, metformin, may offer an alternative therapeutic pathway. Established treatment for painful CIPN is limited. Following recommendations for general neuropathic pain is logical, but evidence for agents like gabapentinoids and amitriptyline is weak. The only agent currently recommended by the American Society of Clinical Oncology is duloxetine."

This 2018 review of various chemotherapy-induced neuropathy treatments does not include the present method, and current methods are cited as less evident [80].

"26 treatment options were identified in 35 studies. Among these, 7 successful RCTs, 6 failed RCTs, 18 prospective studies, and 4 retrospective studies were included. The included studies examined not only pharmacological therapy but also other modalities, including laser therapy, scrambler therapy, magnetic field therapy, and acupuncture, etc. Most included studies had small samples and short follow-up periods. Primary outcome measures varied widely among the included studies. No study was terminated early due to its adverse effects…Evidence is considered of moderate benefit for duloxetine. Photobiomodulation, known as low-level laser therapy, is considered of moderate benefit based on evidence review. Evidence did not support the use of lamotrigine and topical KA (4% ketamine and 2% amitriptyline). Evidence for tricyclic antidepressants was inconclusive, as amitriptyline showed no benefit, but nortriptyline had insufficient evidence. More research on CIPN treatment is needed with larger sample sizes, long-term follow-up, standardized outcome measures, and standardized treatment time."

This 2008 review states that [81]:

"The effective treatment of established CIPN, however, has not yet been found. Lastly, paclitaxel causes a unique acute pain syndrome that is supposed to be caused by neurological injury. No medication has been proven so far to prevent this toxicity. Therefore, this study is justified by the absence of proven efficiency of various methods as well as by the relativity with which various causes may require different approaches."

It is worth noting that chemotherapy toxicity affecting the liver and that this clinical trial recommends L-carnitine for cramps related to liver cirrhosis, 1200 mg/day [82], also recommended by another trial in cramps induced by stroke [83].

"Consecutive patients with cirrhosis and muscle cramps received L-carnitine 300 mg, 3 times/day (900 mg/day, n = 19) or 4 times/day (1200 mg/day, n = 23) for 8 weeks. The frequency of muscle cramps was assessed through questionnaires, and the degree of muscle cramp was assessed through the visual analog scale (VAS). Muscle cramps were reduced in 88.1% of all individuals at the end of the 8-week study period and disappeared in 28.6% of patients."

Such justifications were presented in the previous study of important contributions to the overall health of the patient: [42]

"Recent research has emphasized the importance of ion transfer regarding the elimination or neutralization of free radicals from injured regions in oxidative stress (CHEVALIER; MELVIN; BARSOTTI, 2015; OSCHMAN, 2009; CHEVALIER; MORI; OSCHMAN, 2006; OBER, 2003). The interaction of free radicals with the biological system, also called oxidative stress,

can sometimes result in significant health consequences, contributing to the development of certain pathologies associated with aging, as well as the aging process itself (OSCHMAN, 2007; HALLIWELL; GUTTERIDGE, 1985). This phenomenon helps to understand how patients with inflammatory conditions, treated with the stimulation of migration of electrical charges at sites of acute or chronic inflammation, show improvement in their conditions, preventing "collateral damage" to healthy tissues near a lesion (SOKAL *et al.*, 2013; OSCHMAN, 2009; GHALY; TEPLITZ, 2004). Given this reality, this study aims to evaluate a technology for reducing ionic charges in the impact of joint pain, muscle pain, and cramps in patients with SPP."

15. Discussion

Despite the satisfactory results, we highlight the various available techniques, as having potential in one case or another, under the multifactorial nature of causes and relationships with the patient's nervous and electrochemical structure and the treatment received, having greater weight, such as the simple act of training the muscle, stretching, or triggering certain frequencies increasing its cramp threshold as a preventive measure; being able to be added to certain cases for which a single method did not solve. We must also discuss modern lifestyle with its types of shoes, apartments, and cars, which isolate our feet from contact with the earth, generating accumulation of electrostatic charge and its deleterious effects on human health and overall quality of life, since this is "a factor that predisposes to pain is the change in the electrical environment, the alteration of the pH of biological fluids, and the distribution of charges on molecules. Therefore, direct contact of the human body with the earth or with the use of a metallic conductor affects physiological processes" [61].

16. Conclusions

The efficiency of the product "Magicramp® Peripheral Neuropathy Reducing Pad" (MECRC), in the double-blind randomized clinical trial was evaluated based on the analysis of the Predictive Value (PV). The PPV of 84.6% indicates that most patients who used the product experienced a real reduction in cramps, confirming its effectiveness. However, the NPV of 12.5% reveals the presence of false negatives and true negatives, indicating that the product may not be effective for all patients, and that other aspects were at play (among them psychosomatic ones).

We conclude that the various causes of cancer have various preventive proposals, applicable to CIPN such as increasing the action potential threshold through frequencies and/or stretching, and treatments using various drugs with duloxetine being the most official recommendation (despite its deleterious side effects). Regarding the present study pointing to grounding as a possible solution, we realize that stretching prevents cramps by increasing the action poten-

tial threshold although it may not always be feasible, especially in the context of an oncology patient, and the same happens if certain frequencies are given as recent clinical trials pointed out [62] [63], these also increase the action potential threshold increasing tolerance for muscle contraction. Concurrently and as both a preventive and therapeutic measure, Magicramp® pads, by reducing imposed electrostatic charges, contribute to avoiding even further triggers for cramps in the face of any electrochemical stimuli, even though this is higher and more relaxed due to such preventive techniques. Therefore, this technique is highly recommended for this main aspect, and for other benefits listed here.

Conflicts of Interest

Clinical Trial Funding Declaration: We, the undersigned, authors of the scientific article entitled "Evaluation of the Efficiency of the Ionic Load Reduction Device for Cramps Resulting from Chemotherapy-Induced Peripheral Neuropathy (CIPN) and/or Treatments that Cause Muscle Ion Imbalance and Sudden pH Changes: A Double-Blind, Randomized Clinical Trial," which presents the results of a clinical trial involving a device for the treatment of cramps in patients undergoing oncological treatments, hereby declare the funding received for the conduct of this study. We would like to clarify that the following payments were exclusively made to the clinical trial coordinator, Sodré Gonçalves de Brito Neto, and not directly to the other authors: 1) Research grant: The clinical trial coordinator received all devices free of charge and a research grant of $400 per month, provided by "Efinat - Manufacturing and Trading of Therapeutic Products Ltd." This research grant was intended to cover the costs related to the study, including participant recruitment, data collection and analysis, laboratory and administrative expenses. 2) Payment for publication of results: The clinical trial coordinator will receive a one-time payment of $6000 for the publication of the results, regardless of the study findings or any other related factors. This payment was made by "Efinat—Manufacturing and Trading of Therapeutic Products Ltd." as an acknowledgment of the work conducted and is not contingent upon any specific outcome or favorable conclusion regarding the tested product. We emphasize that the aforementioned payments to the clinical trial coordinator did not influence the impartiality of the other authors in conducting the study, analyzing the data, or disseminating the results. We maintained scientific integrity, ensuring that all information presented in the article is based on solid evidence and in accordance with best scientific practices. We further declare that none of the funders had any control or influence over the study design, data collection, analysis and interpretation, or the writing of the article. Location: Goiânia, Goiás, Brazil Date: 27/03/2024 [Sodré Gonçalves de Brito Neto] [Clinical Trial Coordinator/Undergraduate in Geology and Multidisciplinary Free Nucleus] [UFG] [Hector Lutero Honorato de Brito Siman] [Biostatistics Data Analyst/Biomedical Scientist] [UNE-BH] [Geraldo Silva Queiroz] [Principal Investigator and Mentor/Physician] [ACCG] Data Access The raw data and

detailed research results are available for public access through the following link: [https://wp.me/pccsLB-3j5]. The Excel spreadsheet available at this link contains relevant information about the data collected during the study, including results and participant details. For ethical reasons and in compliance with privacy guidelines, names, social security numbers, identification numbers, and other personal data have been omitted from the spreadsheet. Funding: This clinical trial was funded by the Goiás Cancer Combat Association (ACCG), Naturalweb Ltda, and Efinat Manufacturing and Trading of Therapeutic Products Ltd. The ACCG waived study fees and facilitated patient access through their directors. Naturalweb Ltda and Efinat Manufacturing and Trading of Therapeutic Products Ltd provided financial support, including materials and resources necessary for testing the Magicramp pads, and also awarded a grant to the researcher and study coordinator. All funding sources were used exclusively for research purposes, ensuring the integrity and impartiality of the study.

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