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Pulsed Electromagnetic Field (PEMF): Effective Adjuvant Therapy in Venous and Vasculitic Leg Ulcers

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Abstract

Background: Chronic leg ulcers occur in 1% of the adult population with considerable associated morbidity and tend to follow a chronic course of recurrent healing and breakdown. Venous insufficiency is the commonest cause of chronic leg ulcers in the community, but vasculitic ulcers are known to be more resistant to treatment and also more painful than ulcers of other aetiologies. A proportion of leg ulcers will heal on conservative treatment, those which do not respond cause considerable distress. Many modalities have been used for conservative treatment of leg ulcers and pulsed electromagnetic field (PEMF) was used for wound healing as it has a number of well-documented physiological effects on cells and tissues.

Patients and Methods: A total of 48 patients with 53 resistant venous and vasculitic leg ulcers unresponsive to medical treatment were enrolled in this study. The patients were randomly divided into control group who received standard wound care and active (study) group who received standard wound care plus active (PEMF) therapy 3 days per week for 12 weeks for a total of 36 sessions. Ulcer size, appearance of the ulcer and surrounding skin, and pain intensity were assessed at the entry of the study, at 6 weeks and at the end of the treatment.

Results: At week 12 the active group showed a 56.4% reduction in the ulcer surface area for venous ulcers, and 48.6% for vasculitic ulcers compared to only 17.2% in controls (P=0.01, 0.007, respectively). A significant decrease in pain intensity was seen in the active group (P= 0.007, 0.006 respectively). No adverse events were reported.

Conclusion: PEMF therapy improve the rate and degree of healing and reduces pain in resistant venous and vasculitic leg ulcers, this suggests that it could be a useful addition as an effective adjuvant treatment to non surgical therapy of leg ulcers. There is need for further studies in a larger population to determine the optimal treatment dose, timing and duration of electromagnetic therapy and applicability of using it in resistant ulcers of other aetiologies.

Key words: Pulsed electromagnetic field therapy (PEMF) - resistant leg ulcers- venous ulcer – vasculitic ulcer

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INTRODUCTION

Leg ulceration is a common, chronic, recurring condition and causes considerable morbidity in the adult population. The prevalence of leg ulcers has been estimated by about 1% of the adult population in western countries[1]. Leg ulcers are associated with pain, immobility, social isolation and embarrassment. Pain is considered by patients to be the worst aspect of having an ulcer[2].

There are over 40 reported causes of leg ulceration, however, most ulcers are related to vascular diseases such as venous

disease[3]. A hospital based study in Egyptian population, has found prevalence of venous ulcer to be 2.4%, pain was present in 69% of patients with leg ulcers, psychological distress was present in 28%, restriction of daily activities was recorded in about 78% and working activity was changed in 29.5% of patients[4]. The collagen vascular diseases and vasculitis, in particular, are occasionally associated with chronic, relapsing lower extremity ulcerations. Leg ulcers are a recognised manifestation of cutaneous vasculitis in connective tissue diseases (CTDs) including rheumatoid arthritis (RA)[5], scleroderma, lupus erythematosus[6].

Patients with RA are predisposed to developing chronic leg ulcers. Approximately 910%- of patients with rheumatoid arthritis will experience leg ulceration[7,8,9], and as many as 10% of leg ulcers of any cause[10] and 12% of patients with a chronic venous ulcer can be seen in association with RA or have positive tests for RF[11]. Whereas the exact incidence of leg ulcers in patients with systemic sclerosis (scleroderma) is currently not defined[12], however, some may consider it as the most common collagen disease causing leg ulceration[13]. They may develop leg ulcers of varied aetiologies, including venous disease, infection and inflammation (vasculitis or pyoderma gangrenosum). The leg ulcers in these patients may involve several of these aetiological factors and are often difficult to heal[8,14]. Leg ulceration is one of the cutaneous manifestations in Behçet's disease and sometimes is very difficult to treat[15] while, incidence of leg ulcerations was found to be 5 % of SLE patients[16] and can occur in SLE patients with antiphospholipid antibodies and/or vasculitis[17]. Until now, the treatment of leg ulcers in patients with collagen-vascular disease remained rather ill-defined[18].

There is a wide variety of treatments of leg ulcers available which focused on alleviating the local hemodynamic changes include hemodynamic preventive measures, ulcer dressings, topical treatments and surgical or endovascular repair of the microvasculature[19]. But it is generally agreed that elevation of the legs and compression bandaging is of central importance especially for venous ulcers. Pulsed electromagnetic fields (PEMF) have been used in the last years mainly in connection with healing of bone fractures, burns, wounds, and in treatment of various acute soft tissue injuries[20] and it is becoming more and more widely accepted as an alternative method for treatment. In such conditions, not only magnetic field therapy aids in recovery, but also, it allows these conditions to heal better, more quickly, and with less scar tissue. Magnetic treatment has been shown to decrease healing time by half or more[21]. Many clinical trials have shown that electrical stimulation of skin accelerates wound healing by augmenting the endogenous current induced by injury[22,23], electric or magnetic fields may accelerate wound healing only under circumstances in which healing process is delayed or arrested, i.e. conditions of deficient or absent electrical current[24]. PEMF have an advantage over the electric current in that the electromagnetic signals penetrate the dressing and the tissue involved.

In short, pulsed magnetic fields interact with electrically conductive elements in tissue, resulting in induced currents. The basic mechanisms underlying the clinical effects of PEMFs are not clear. However, it has been suggested that PEMF, by altering or augmenting pre-existing endogenous electrical fields, may trigger specific, measurable cellular responses such as DNA synthesis, transcription and protein synthesis[25].

Aim of the work:

To study the effect of exposure to pulsed electromagnetic fields (PEMF) on the rate of healing of resistant leg ulcers.

PATIENTS AND METHODS

This study was designed as a prospective, randomized controlled clinical trial, to evaluate the efficacy and safety of, the PEMF therapy as an adjunctive treatment for recalcitrant leg ulcers. A total of 48 patients with resistant leg ulcers unresponsive to medical treatment were recruited from Outpatients clinics of Vascular Surgery unit and Rheumatology & Rehabilitation department of Mansoura University Hospitals and enrolled in this study. For inclusion into the study, the patient's ulcer should have demonstrated unsatisfactory healing for at least the previous four weeks and were under medical care prior to entry in the study.

Patients were excluded by the absence of a pedal pulsation or by the presence of ischaemic skin changes. Patients known to be suffering from malignancy, or had cardiac pacemakers in situ or had a deep venous thrombosis within the past year or congestive heart failure, hepatic or renal failure, or pregnant women were also excluded.

Patients were divided into two groups; group A (study group) received active treatment and further subdivided into; group A1 which included twenty patients with chronic venous leg ulcer (diagnosed according to Standards recommended by the Society for Vascular Surgery/North American Chapter and the International Society for Cardiovascular Surgery as criteria to define chronic venous leg ulcer[26] and group A2 which included fifteen patients with collagen vascular disorders with a total of 18 ulcers (6 patients with RA, 5 patients with scleroderma, two patients with SLE, and two patients with Behçet's disease) who fulfilled the American College of Rheumatology criteria for each disease[27,28,29,30] and group B (control group) included thirteen patients with a total fifteen ulcers (8 patients with venous ulcer, two RA patients, two scleroderma patients, and 1 patient with Behçet's disease).

Thirty-five patients were randomized to the active treatment group and 13 patients to the control group. The control group were randomly allocated to receive standard wound-care treatment only, while The active group patients received standard wound-care and were treated by a course of PEMF therapy which was provided using commercially available apparatus, Magnetic Bio stimulation Device mbs-system: (G-pulse 210μp) applied by coil. PEMF therapy applied with intensity equal to 3mt and frequency of magnetic field impulses equal to 4 Hz. All patients in the active treatment group received a 30-minute treatment session

three days per week for 12 weeks for a total of 36 sessions. This was followed by a 4-week observation period with dressing changes only. Patients' previous dressing regimens remained unchanged during the trial. However, if healing ulcers required fewer dressing changes, due to a decrease in exudate, a more suitable dressing was applied. Patients were allowed to continue systemic treatments for rheumatoid arthritis, scleroderma, Behcet's and lupus.

Assessment of the outcome of treatment was based on the parameters measured on the day of admission, at six weeks, and at the end of the treatment included ulcer size (calculated from the maximal length and breadth measured by cm), photograph of the leg, appearance of the ulcer and surrounding skin, characteristics of the border (presence of inflammation around the edges and on the surrounding skin, vascularisation, detaching, necrosis), presence of spontaneous or contact pain, pain intensity on a visual analogue scale (VAS), and presence of complications.

The Statistical Package for the Social Sciences (SPSS) versions 10 (SPSS Inc.; Chicago, Illinois, USA) under the platform of Microsoft Windows XP, was used for analysis of data and for descriptive statistics (mean $\pm$ SD, and ranges). Pretreatment versus post treatment differences were analysed for statistical significance by using paired t tests, relation between variables were investigated by Pearson's correlation coefficient. P value less than 0.05 was considered statistically significant.

RESULTS

No statistically significant differences were found between the treated groups prior to treatment in all parameters measured, as shown in Table (1).

Table 1: Demographic Data of the studied groups (no of ulcers = 53).

	A1 (n = 20)	A2 (n = 18)	B (n = 15)
Sex M/F ratio	14/6	10/8	8/7
Age- Mean $\pm$SD Range (years)	52.8 $\pm$ 11.76 33-72	54.72 $\pm$9.56 37-71	49.93 $\pm$10.48 32-68
Duration of ulceration- Mean $\pm$SD Range (weeks)	32.5 $\pm$24.22 8-86	43.78 $\pm$26.54 15-102	31.6 $\pm$21.19 8-77
Initial Mean ulcer size - Mean $\pm$SD Range (cm^2)	13.96$\pm$16.75 2.1-57.85	19.81$\pm$23.38 2.16-69.3	15.49 $\pm$11.72 2.85-42.75

Means of the present ulcer duration were 32.5, 43.78 and 31.6 weeks for groups A1, A2 and B respectively. Mean ulcer sizes at the entry of the study were 13.96, 19.8 and 15.5 cm^2 for groups A1, A2 and B respectively. Three patients in group A2 and two in group B had multiple leg ulcers, all included in the study.

Changes in ulcer area

When the ulcer size was studied, the mean area of the ulcers at the initial assessment did not differ significantly between the three groups. After 6 weeks, some ulcers had completely healed in groups A1 (5 (25%) ulcers) and nearly healed in group A2 (2 (11.1%) ulcers) but none in group B. This trend for healing was better in group A1 than groups A2 and B, compared to the initial assessment visit. Percentage mean reduction was 43.5% in group A1, 26.7% in group A2 and 6.2% in group B and significantly different between groups A1, A2 and B ($P < 0.001$).

By the end of the treatment phase, after 12 weeks, 7 (35%) ulcers in group A1 (Figure.1), 4 (22.2%) ulcers in group A2 (Figure 2) and only 2 (13.3%) ulcers in group B had completely healed, whereas, 10 (50%) ulcers in group A1, 7 (38.9%) in group A2 and only 2 (13.3%) in group B had shown a reduction of 50% in the ulcer area. The reduction in the ulcer area from the initial assessment was significant in groups A1 and A2 ($P<0.001$, $P=0.004$, respectively). Percentage mean reduction was 56.4% in group A1, and 48.6% in group A2 compared to only 17.2% in group B and significantly different between groups A1, A2 and B ($P <0.01$, $=0.007$, respectively) (Table 2, Figure.3). In both active subgroups, there were significant negative correlations between the initial size of the ulcer, ulcer duration and the percentage change in the ulcer area ($P< 0.02$, $= 0.007$) for the venous ulcers and ($P< 0.05$, 0.02) for the vasculitic ulcers.

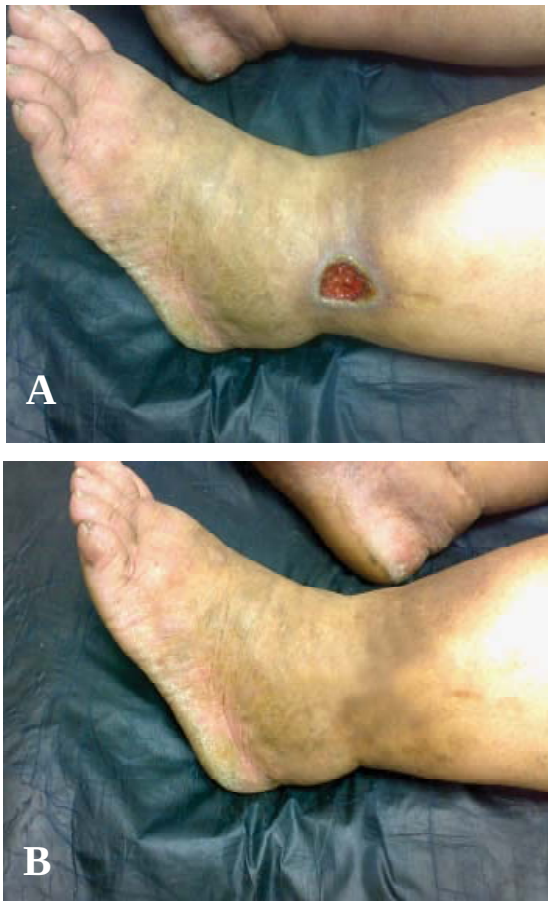

Fig. 1: Venous ulcer (A) at the enrollment of the study. (B) at the end of the treatment.

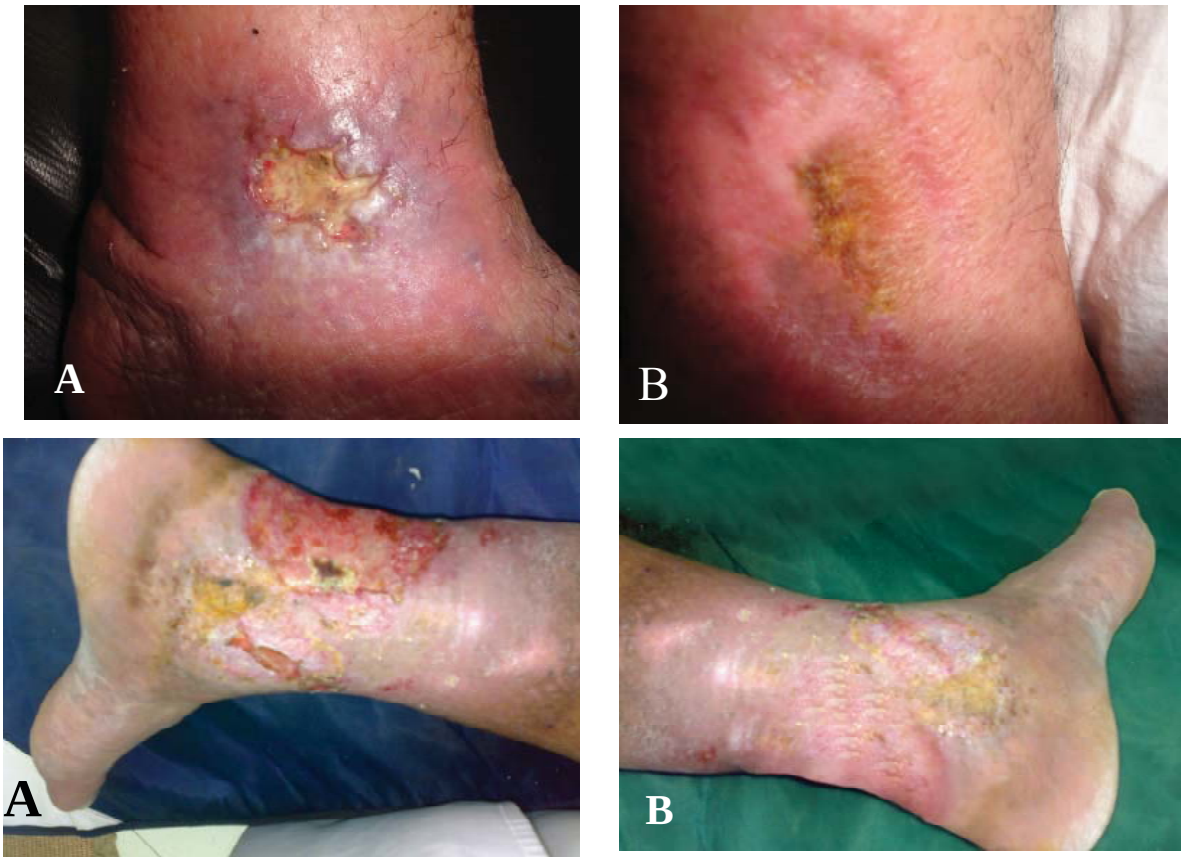

Fig. 2: Vasculitic ulcer (A) at the enrollment of the study. (B) at the end of the treatment after 12 weeks.

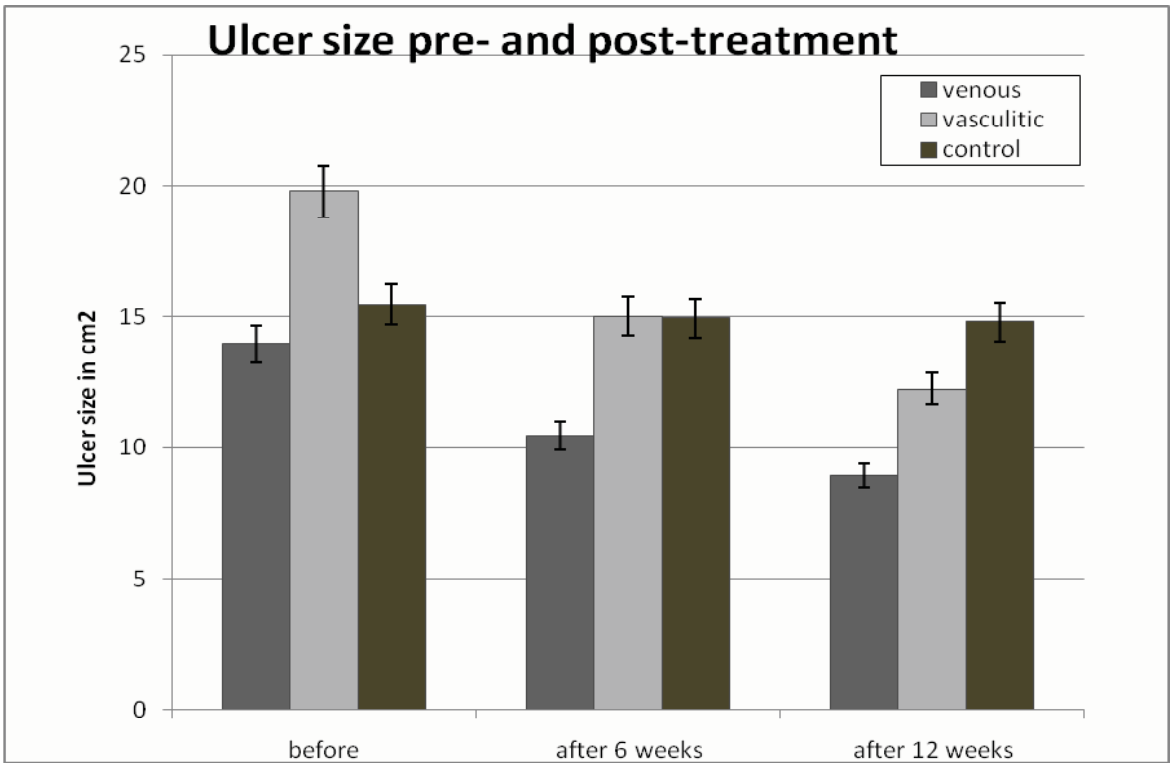

Fig. 3: The size of the ulcers in the studied groups prior to treatment, at 6 weeks and after the end of treatment.

Table 2: Mean ulcer sizes pre and post treatment in cm^2 .

	Group A1	Group A2	Group B
Baseline area	13.96 ±16.75	19.81±23.38	15.49 ±11.72
After 6 weeks area	10.45 ± 14.5	15.02 ± 17.48	14.96 ± 11.85
Post treatment area after 12 weeks	8.96 ± 13.49	12.25 ± 14.8	14.81 ± 12.73
Percentage reduction in ulcer size			
After 6 weeks	43.45	26.73	6.17
After 12 weeks	56.36	48.6	17.15

Pain at the ulcer site

There were significant reductions in pain scores from start day to end day with the larger decrease in pain being in groups A1 and A2 (P< 0.001) with a mean reduction of 2.05 (61.17%), and 2.11 (54.28%), respectively and a reduction of only 0.47 (14.46%) (not significant) in group B (Table 3, Figure. 4).

Table 3: Mean ulcer pain scores read from analogue scales.

	Mean pain score	Range of mean values
On the entry of the study		
Group A1	4.4 ± 2.3	0-8
Group A2	4.61 ± 2.2	2-8
Group B	5.6 ± 1.99	2-9
After end of treatment		
Group A1	2.35 ± 2.46	0-8
Group A2	2.50 ± 2.04	0-6
Group B	5.13 ± 2.88	0-9

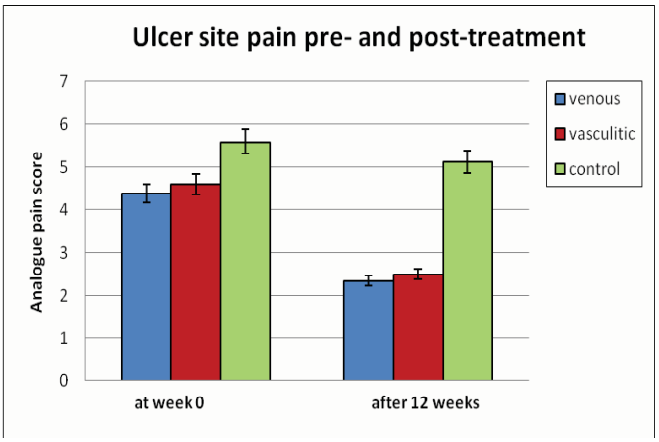

Fig. 4: The ulcers' site pain score in the studied groups prior to treatment and at 12 weeks after the end of treatment.

DISSCUSION

Vasculitic necrosis and ulceration of the skin are frequent complications of connective tissue diseases and are very difficult to heal[31], as it may rapidly extend widely and deeply. Many vasculitic ulcers fail to respond to conservative treatment, and patients have to be admitted for long periods of bed rest, cleansing, ulcer excision and repeated skin grafting which often fail to take. Procedures that increase blood flow such as adjuvant prostacyclin infusion or lumbar sympathectomy may help[32]. A common vasculitic ulcer occur in RA, the causation of leg ulcers in patients with RA was found to be multifactorial-predominantly a mixed vasculitic and venous aetiolog [33]. A proportion of rheumatoid ulcers will heal on conservative treatment, those which do not respond cause considerable distress and may end by the demand for amputation[34]. In short, vasculitis leg ulcers are an interdisciplinary therapeutic challenge. On the other hand, there is a paucity in alternative non-surgical therapies for ulcers that do not respond to conventional treatment that increases the need for new modalities in treatment, meanwhile, PEMF has been used to promote wound healing with a growing increase of data demonstrating its biological effects[35]. So, this was a motive to design this study to assess whether low-frequency PEMF has a beneficial effective role as an adjuvant to non-surgical management of resistant leg ulcers.

RA patients with persistent leg ulcers tend to have long-standing, seropositive, erosive disease with a mean duration of open ulceration of 5-15 months[36,37]. This compares with a median duration of 6 months in patients with venous ulceration[11] Although treatment regimes were not strictly comparable, these Figureures support the notion that ulcers in patients with RA are more resistant to treatment[8]. This was confirmed by our results.

The results of this study showed that PEMF stimulation had decreased the ulcer area by 61.2% of venous ulcers, and 54.3% for the vascultic ulcers after 12 weeks of treatment in patients who received active treatment. These were consistent with the study of Ieran et al.[38] who found significant wound healing in patients being treated with pulsed electromagnetic therapy at 75 Hz after a 90-day treatment period: healing was within 71 days on average. Another study of Stiller etal.[39] in which leg ulcer patients were treated with pulsed electromagnetic fields, a significant improvement in the healing of leg ulcers with a 47% decrease in ulcer area was recorded in the active group against a placebo group. Also in the study of Kenkre et al.[40] who applied electromagnetic field therapy to long-standing venous leg ulcers resistant to routine therapy and reported that percentage mean reduction was 63% in patients who received active PEMF therapy. More recently, Cañedo-Dorantes et al.[41] found that after exposure to low frequency electromagnetic fields, the responders in their study showed healing velocity between 0.3-3% of their leg ulcers.

Moreover, 50% of venous ulcers, and 38.9% of vasculitic ulcers had shown a reduction of 50% in ulcer area. Cañedo-Dorantes et al.[41] in their study classified their patients into responders who showed healing of the wounds or had a > 50% size reduction during the treatment period and they were 69%.

In a study by Sarma et al.[42], planter ulcers were treated by exposure to pulsed magnetic fields yielded a decrease in the volume of 40% or more in 89% of patients and they strongly suggested that exposure to PMF causes a significantly more rapid healing of plantar ulcers.

It is also noteworthy in our study, that 35% of venous ulcers and 22.2% of vasculitic ulcers received active PEMF had completely healed by the end of the treatment. Stiller et al.[39] stated that half of the PEMF-stimulate ulcers healed or improved markedly. Also, Kenkre et al.[40] found that in all groups they studied some ulcers healed despite having long histories.

In the present study, the control group exhibited a 17.2% reduction in size. Ieran et al.[38] reported significant spontaneous healing in their control. Our findings coincided with those of Ieran's and also with Kenkre et al.[40] study who reported 34% percentage mean reduction in their placebo group. However, Stiller et al.[39] found that the control group in their study exhibited a 48% increase in wound area, they explained that by the stringent protocol inclusion-exclusion criteria they followed and because their study sites were tertiary referral centers making the ulcers in their study particularly recalcitrant.

An important factor in the pathogenesis of venous ulcer, is increased production of oxygen free radicals and lipid peroxides by both the trapped white cells due to reduced perfusion resulted from increased venous pressure[43], and by the cutaneous iron overload from the extravasated RBCs. Those in turn will produce endothelial damage and tissue destruction[44]. Recent study has reported that PEMF had reduced lipid peroxidation, increased antioxidants production to stimulate endogenous defense against free radicals and protected cells against O_2 toxicity and cellular lysis[45].

Inflammatory process is the main contributing factor in vasculitic ulcer. Earlier studies have shown that PEMF has significant antiinflammatory effect. Though the exact mechanism by which PEMF exhibits such effect is not clearly understood, the cell membrane is most often considered as the main target for PEMF signals[46]. Oxidative stress and defective antioxidant defense system could cause lipid peroxidation of cellular membranes, resulting in inhibition in the activities of Ca_2+-ATPase which, in turn, could increase intracellular concentration of Ca_2+ which could activate phospholipase A2, which, in turn resulted in release of arachidonic acid and production of PGE2[47], which plays a major role in inflammation. Recently, it has been found that PEMF could stabilize the membranes subsequently restoring the membrane protein activity (Ca_2+-ATPase) thereby maintaining intracellular Ca_2+ level at extremely low level. This, in turn, decreases the inflammatory PGE2 levels and consequently suppressed the inflammation[45]. PEMF has also a number of well-documented physiological effects on the immune system as it amplifies the phagocytic activity of polymorph nuclear leukocytes, increases the number of circulatory neutrophils and enhances the formation of antibodies[48].

Modification in cellular calcium has been implicated in other several biological effects of PEMF. These include rapid alteration in cell permeability, oxygen tension and cAMP and increased collagen synthesis[35,49]. It has been also, reported that PEMF stimulation decreases the doubling time of fibroblasts and endothelial cells and induces differentiation of skin fibroblasts in culture[50]. Increased collagen synthesis, angiogenesis[51,52], and bacteriostasis are some mechanisms by which PEMF may contribute to wound healing.

Chronic ulceration of varying etiology is frequently associated with accumulation of acute and chronic inflammatory cells around vessels and presence of edema, however, in the gaiter area, where the bone ratio is higher and tissue compliance lower, it is suggested that such changes produce tissue pressure, skin destruction and ulceration[53]. PEMF therapy can reduce the edema by enhancement of the microcirculation. It increases the blood supply to the injured area, increases oxygen pressure and perfusion, as well as capillary blood flow, reducing the accumulation of metabolites in the area and removing of the accumulated lactic acid and waste products[48].

It is well known that normal cells have a basic electric potential about 90 milli-volt (mV) which is necessary for their function. Diseased and damaged cells have altered rest potentials. The increased electrical resistance around injured tissues prevents the low potential capillary ionic flow from entering the zone and enhancing healing. Magnetic fields, however, permeate all cells, regardless of potentials. PEMF influences ions around the injured zone. The rest potential is highly influenced by PEMF. In turn, ionic exchange at the cellular level influences oxygen utilization, needed for healing[54].

Ulcers caused by vasculitis are often described as extremely painful[8,37]. In this study we noted significant reductions in ulcer pain scores for both venous and vasculitic ulcers. Our findings of pain relief after PEMF therapy confirm what was suspected by other researchers[39,40]. PEMF can reduce pain through reduction of inflammation and edema and reduction of PGE2 as mentioned above. Another possible mechanism is that PEMF stimulates opioid receptors and increases the release of endorphins and encephalins at the reticular formation. Also, electromagnetic currents in the treatment area block the painful stimuli either in the receptor level or at cortical or subcortical areas[55].

However, in an earlier study of Todd et al.[20] although they stated that both active and control groups in their study showed an overall reduction in ulcer size over the study period and there was a trend in favour of improved healing in the ulcers treated with the active coils, but they failed to show a statistically significant improvement in the ulcers treated with the active coils. There was no effect on the percentage change of pain between the active and inactive groups. They attributed that to the discrepancy in ulcer duration between the two groups, low inadequate selectivity of the patients with regard to the aetiology of ulceration, or other circumstances, such as the degree of patients mobility and the adequacy of the ulcer therapy on the days not seen in the outpatient department.

We found that one important predictor of ulcer healing was ulcer size—there was a more successful outcome for smaller

ulcers. Another predictor of ulcer healing was ulcer duration. This indicates the earlier the management of the ulcer, the better the outcome.

Regarding the safety of PEMF therapy, no adverse effects were complained by the patients during the study period apart from feeling sleepy after the session which rather considered as a benefit by some patients. This could be attributed to the calming and sleep-inducing effect of PEMF due to stimulation of melatonin hormone, which anti-stressful[56]. These findings coincided with those of Stiller et al.[39], they found no reports of patient complaints or adverse events attributable to the use of PEMF in their study, and also with those of Cañedo-Dorantes et al. [41] who reported that negative secondary effects were absent in their study during treatment and follow-up periods.

On the other hand, in Kenkre et al. study[40], although their patients experienced adverse events during the study but no patients withdrew from the study because of these adverse events and all of the patients in their study tolerated their treatment sessions well. Moreover, these complaints may be irrelevant or related to other associated causes as they occurred in both active and control groups who did not exposed to electromagnetic therapy.

Therapeutic applications of magnetic fields have grown over the last three decades, gaining acceptance in some medical specialties. Electromagnetic therapy provided significant additional gains in the rate and degree of ulcer healing and reduction in pain. We conclude that the PEMF therapy is a safe and effective adjunct to non-surgical therapy for refractory venous and vasculitic leg ulcers. However, there is a need for further studies in a larger population to determine the optimal treatment dose, timing and duration of electromagnetic therapy and applicability of using it in resistant ulcers of other aetiologies.

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