



A randomized controlled trial of electromagnetic therapy on microcirculation and healing of painful vascular leg ulceration.

Eman M. Othman

Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Egypt.

Abstract: The aim of this study was to investigate the efficacy of pulsed electromagnetic field therapy on vascular lower limb ulcers healing and microcirculation. **Methods:** Forty patients (24 females and 16 males) between 45 and 65 years old with vascular leg ulcers were randomly assigned into two equal groups of 20. Both groups received their routine conventional therapy; additionally, Group (A): (N=20) received pulsed electromagnetic field therapy at a frequency of 12.5 Hz, 20 min per session, day after day for 2 months, While group (B) (N=20) received 2 months of routine conventional therapy only. Methods of evaluation were Ulcer Surface Area (USA), Ankle Brachial Pressure Index (ABPI) and Visual Analogue Scale (VAS). **Results:** Results showed significant improvement ($P \leq 0.05$) in USA (3.36 ± 1.3), ABPI (0.85 ± 0.04) and VAS (2.2 ± 0.83) after 2 months of pulsed electromagnetic field therapy (Post 2) for group (A) rather than group (B) as manifested by decreasing pain, ulcer surface area and increasing ankle brachial pressure index. **Conclusion:** Pulsed electromagnetic field therapy is effective in accelerating healing, improving microcirculation and relieving pain of vascular leg ulcers.

Key words: Ankle brachial pressure index– Pulsed electromagnetic field therapy- Vascular ulcers and Wound surface area.

Introduction

Inside the circulatory system, blood streams starting with those large artery downstream to the small artery, afterward with microcirculation in nutritive capillaries, and finally to the venous system. Microcirculation is the main spot to complete transport and exchange of nutritive substances and metabolic wastes among blood and tissue fluid. Therefore, changes of blood streams in microcirculation may play a vital role in pathogenesis of tissue damage in lower limbs¹.

The maldistribution of blood stream among cutaneous capillaries and arteriovenous shunt stream is a vital factor leading to the occurrence of ulcer. Therefore, the recovery of microvascular function is important in stopping non healing wounds in patients with ulcer².

Ulceration because of vascular reasons is often multifactorial and can be as a result of both arterial and venous disease³. Arterial and venous leg ulcers can be referred to as inflammatory approaches produced by means of blood ischemia, tissue anoxia, edema, cellular dying, and infection⁴.

Arterial ulceration may be due to either progressive atherosclerosis or arterial embolization. Each of which cause ischemia of the skin and ulceration⁵. Venous (or stasis) ulceration may be started by venous hypertension that develops due to insufficient calf muscle pump activity and after the onset of either primary (Without an obvious underlying etiology) or secondary (After deep venous thrombosis) valvular incompetence⁶.

Venous ulcer is the practically regular type of lower limb wound, as 80% of leg ulcers have a venous structure⁷, it require months to heal. The natural history of the disease may be a constant cycle of slow healing and repetitive breakdown⁸. The prevalence of venous leg ulcers will proceed to increase because of those aging population and increasing occurrence of risk factors for example, obesity and congestive heart failure⁹. The annual cost of the care and management of the case is high and set to grow exponentially^{10, 11}.

Vascular leg ulcers are related to considerable morbidity and impaired quality of life with healing being a long and painful process¹⁰ both all through and between dressing changes, and throughout surgical excision of dead tissue (Debridement)¹². The cause of pain in human beings with vascular leg ulcers is complicated and regularly poorly described. The pathologies related to leg ulceration (e.g. Rheumatoid arthritis, vascular disease and diabetes) cause pain without or with an ulcer present^{13, 14}. Dressings, topical creams and lotions had been promoted to reduce the pain of ulcers. However, there was insufficient evidence concerning any side effects of these methods and its effect on healing¹².

Many putative therapeutic methodologies for chronic leg ulcer treatment had been proposed, including the utilization of antiseptics, antibiotics, growth elements, pressurized oxygen, biologically engineered skin substitutes, along with physical therapy modalities, for example, ultrasound, electric stimulation, and electromagnetic fields¹⁵⁻²⁰.

Treatment of vascular ulcer through pharmacologic agents and regionally applied growth factors had shown poor results^{21, 22}. A success experimental treatments consist of immediately implemented electromagnetic fields (ELF)^{23, 24}.

Electrotherapy and electromagnetic therapy were had been to treat ischemic, diabetic ulcers and vascular ulcers, respectively, with contrasting findings¹⁶. Electrical or electromagnetic stimulation may be beneficial to increase ulcer healing through their antibacterial impact, stimulating growth factors and collagen synthesis^{24, 25}. Pulsed electromagnetic field (PEMF) is a non-pharmacological and non-invasive therapy that may be implemented on the affected body part, which penetrates via skin and reaches target tissues¹. Pulsed magnetic field therapy can stimulate peripheral blood mononuclear cells (PBMCs), which can be able to accelerate wound healing after being transported to the ulcer site via the blood²⁶. In human beings, it had been proven that magnetic fields implemented at a site a long way from the lesion can allow wound healing in chronic leg ulcers and activate angiogenesis^{26, 27}. Also, PEMFs had also been useful in treatment of chronic pain related to connective tissue (Cartilage, tendon, ligaments and bone) injury and joint-related soft tissue injury^{28, 29}.

Therefore, this study was examined the effectiveness of electromagnetic therapy for promoting the healing of vascular ulcers in terms of enhancing wound closure, facilitating microcirculation and decreasing pain.

Materials and Methods

A prospective, randomized, parallel groups, active controlled study with a 1:1 allocation ratio was conducted from Aug. 2015 to Jun. 2016 at the research laboratory unit of the Faculty of Physical Therapy, Cairo University. Patients of both genders (24 females and 16 males) with unilateral chronic vascular (Arterial or venous) grade II lower limb ulcers according to Wagner-Meggitt classification of ulcer³⁰ and its duration ranged from 2-3 months after the presence of ulcer. Patients were recruited from the Outpatient Clinics of Kasr El-Aini Hospital, Cairo University. The patients participated in the study after signing an informed consent form prior to data collection. The subjects were chosen under the following criteria: Their ages were ranged from 45 to 65 years old. All patients should understand and follow the instructions. Patients were clinically and medically stable and free from any medical problem that may affect the outcomes. All patients were conscious and ambulant. All patients had received their routine conventional therapy, including debridement, systemic antibiotics, wound cleaning with normal saline, offloading (Pressure relief) and daily wound dressings. Patients were nonsmokers, not alcohol drinkers, were under own prescribed medications, and controlled diet therapy

described by their physicians. The exclusion criteria included the following: Patients who had cardiac abnormalities or cardiac pacemakers. Those who had previous surgical procedures in lower limb which may affect the study. Subjects with life threatening disorders as renal failure, myocardial infarction. Patients suffering from skin disease and/or any disease that can lead to ulcer other than diabetes as varicose veins, trauma and peripheral vascular diseases. Those who were presented with active malignancy. Patients suffering from myasthenia gravis, hyperthyroidism, hemorrhage, acute viral diseases, acute tuberculosis, mental disorders, soft tissue infection, cellulites, swelling or those with pacemakers. Ulcer with surface area less than 2 cm² or more than 8 cm² ⁽³¹⁾. After an extensive medical screening when a physician checked the in- and exclusion criteria, eligible participants were randomly assigned via a balanced assignment to group (A): (N=20) who received pulsed electromagnetic field therapy (PEMFs) in addition to routine conventional therapy through the treatment period at a frequency of 12.5 Hz, 20 min per session, 3 times per week for total period of 2 months, and group (B): (N=20) who had received only the same routine conventional therapy. The groups were balanced for eligibility by simple randomization with generated sequence of letters (From a table of correlatively ordered permutations) for each category and combination of categories. The sequences assigned to the patients were placed in envelopes containing the allocation to each study group. An independent person who was blinded to the research protocol and not otherwise involved in the trial operated the random assignment.

Procedures

Before the beginning of the study, personal data were taken from all patients. In addition, they were asked about any history of previous lower limb surgeries, and injury (Past history). Detailed analysis of the present ulcers had been carried out by physician (Present history). Medical history including drugs in actual use especially anti-diabetic drugs had been considered. The physical examination included general examination, and local examination of lower limb which had been carried by staff of physicians. Routine laboratory investigations, mainly fasting and postprandial blood glucose had been carried out.

*Pulsed electromagnetic field therapy (PEMFs) procedure:

The therapy protocol had been attained by pulsed electromagnetic field therapy unit (JAMAVA® S Magneto therapeutic apparatus) the manufacture of the JAMAVA equipment was certified with the aid of the ministry of the Czech Republic and Ministry of health of the Slovak Republic and also was accepted by State institute of drug control, Prague, Czech Republic, Electrotechnical testing institute, Prague, Czech Republic, Testing institute of medical equipment LGA Nürnberg, Germany, State institute of drug control, Bratislava, Slovak Republic, Electrotechnical testing institute and Banska Bystrica, in addition to Slovak republic^{32,33}.

All patients in both groups (A) and (B) would receive the same medical conservative treatment would be comprised of:

- 1- Systemic antibiotics according to culture tests.
- 2- Debridement: for the removal of the dead necrotic tissues and foreign bodies when needed.
- 3- Irrigation of the wound by normal saline then washed by betadine solution once daily.
- 4- Dressings: after irrigation of the ulcer, it had been covered by sterile Vaseline gauze (Sofra-tulle dressing) as all dressings had been changed once daily³⁴.

The pulsed electromagnetic field treatment (PEMFs) was implemented for 20 minutes over the vascular ulcer immediately with the patient positioned in a relaxed position, consistent with the site of ulcer, where the affected leg was raised on a pillow covered with sterile towel. Active surface of the JAMAVA equipment was fixed directly over the sterile Vaseline gauze (Sofra-tulle dressing) via a strap across the leg. Also, active surface of the equipment was covered with disposable Cling's film to avoid cross contamination between patients³⁵. PEMFs connected toward a program (2): Mild impulses, calming North polarity of the magnetic pulses with frequency of 12.5 Hz along with buttons 1, 2, 4 and 5 down while buttons 3 and 6 up^{33,36}.

*Outcome Measures

Both groups underwent identical tests for three times: Before the first session (Pre), after 1 month of initiation of treatment (Post 1) and after 2 months of initiation of treatment (Post 2). Those tests were Ulcer Surface Area (USA), the Ankle Brachial Pressure Index (ABPI) as primary outcomes of the study and a Visual Analogue Scale (VAS) as a secondary outcome of the study.

- Measurement of Ulcer Surface Area (USA):

This method of measurement was performed by using tracing for the ulcer surface area using the graph paper technique according to Kitchen and Bazin,³⁷ in the following steps: A sterilized transparency film was positioned immediately over the ulcer (After rinsed it with antiseptic solution), and the ulcer perimeter was traced with a fine tipped pen. Three tracing of every ulcer was made at every measurement session via the same investigator to establish measurement reliability through obtaining the mean of those three measurements. Then the traced transparency film became positioned over carbon paper with a white paper in between, and transcribed the tracing onto metric graph paper, and the number of 1 mm² in the ulcer tracing was counted (Only full 1 mm² within the perimeter was counted, and the site was converted to cm²). This approach was used to measure the area of an ulcer to calculate the percentage of changing in ulcer area among the same patient and calculate the difference between patients in both groups³⁸.

- Measurement by Ankle Brachial Pressure Index (ABPI):

The ankle-brachial pressure index (ABPI) was a basic and standard test for the evaluation of arterial disease. The following steps summarize the procedures for obtaining an ABPI:

1. A blood pressure cuff and a Doppler were the 2 pieces of equipment needed.
2. The patient was asked to lie in a supine position for approximately 10 minutes.
3. The brachial blood pressure was measured on both arms. The higher of the 2 systolic pressures was the denominator in the equation.
4. A blood pressure cuff was placed around the leg above the ankle. The dorsalis pedis and posterior tibial artery pulse was palpated, and then transducer gel was applied on the skin over the arteries. The Doppler probe was placed over one of these arteries to identify a signal.
5. The blood pressure cuff was inflated and carefully deflated until a sound was heard. This was the ankle systolic pressure and becomes the numerator in the equation.
6. Calculate the ABPI by dividing the brachial into the ankle pressure. Results were interpreted as follows:
 - Above 0.9 – normal, asymptomatic.
 - 0.71 to 0.9 – mild disease, claudication.
 - 0.41 to 0.70 – moderate disease, claudication.
 - Below 0.40 – severe disease, rest pain.

- Measurement by Visual Analogue Scale (VAS):

- The Visual Analogue Scale (VAS) consists of a line, usually 10 cm long, whose ends were labeled as the extremes of pain (e.g., No pain to unbearable pain)³⁹.



- Patient was asked to place a mark on at the point on the line which best represent their experience of pain between "no pain" to "worst pain", then the operator measured the separation starting with the zero "no pain" in millimeters³⁹.

Visual Analogue Scale can be taken into consideration to have ration scale properties, scored fast to give feedback to the clinician, sensitive to treatment outcomes, and good proof for the reliability and repeatability for each effective and intensity scales. The reliability of VAS was the greatest and its validity was the highest among other pain scales⁴⁰.

Statistical procedures

All statistical measures were carried out using the Statistical Package for Social Studies (SPSS) version 22 for Windows (Armonk, NY: IBM Corp). In this study, the mean and the standard deviation was calculated for all patients (Both groups of the study) after the detected time of the study. Descriptive statistics and a t-test were used for comparison of the mean demographic data between both groups.

- Paired t-test to compare the variable within each group to detect level of significance in each group.
- Unpaired t-test to compare the variable between groups was used to detect significance level between the two groups (Comparison).
- Both the descriptive and the analytic statistical were used to examine, describe and analyze the collected data in order to detect if there were any inter group differences before and after treatment application A value of $P < 0.05$ was considered statistically significant⁴¹.

Results

I- Statistical analysis of age

The demographic characteristics of the patients were shown in Table (1) which indicated that there was no significant difference in both groups ($P > 0.05$) in comparison of mean values of age in both groups (A & B).

Table (1): The statistical analysis of age in years between both groups of the study.

Statistics	Age (years)	
	Group (B) (N=20)	Group (A) (N=20)
Mean± SD	56±5.5	55.9±5.9
T. value	0.2	
P. value	0.9 ^a	

SD= Standard deviation, P-value= Probability level, ^a=Non-significance.

II- Results of Ulcer Surface Area (USA) measurement in cm², in group A (PEMFs group).

As observed in table (2) and figure (1), there was a highly significant decrease between means of the post (1) records (After 1 month of the treatment with PEMFs) and the pre-treatment records ($P < 0.05$). Also there was a highly significant decrease between the means of the post (2) records (After 2 months of treatment with PEMFs) and the pre-treatment records ($P < 0.05$). As well as there was a highly significant decrease between the means of the post (2) records and the post (1) records ($P < 0.05$).

Table (2): The statistical analysis of the 3 records of USA in group A (PEMFs) in cm².

Statistics	Ulcer Surface Area (USA) in cm ²					
	Post (1)	Pre	Post (2)	Pre	Post (2)	Post (1)
Mean ±SD	5.77±1.56	6.98±1.36	3.36±1.3	6.98±1.36	3.36±1.3	5.77±1.56
T. value	-8.42		-15.54		-10.35	
P. value	0.0001 ^b		0.0001 ^b		0.0001 ^b	

SD= Standard deviation, P-value= Probability level, ^b= Significant difference.

III- Results of USA changes in cm², in group B (Routine conventional therapy application only).

As observed from table (3) and figure (1), there was a significant decrease between means of the post (1) and pre-treatment records ($P < 0.05$). Also there was a significant decrease between means of the post (3) and pre-treatment records, as well as between means of the post (2) and post (1) records ($P < 0.05$).

Table (3): The statistical analysis of the 3 records of USA; in group B (Routine conventional therapy application) in cm².

Statistics	Ulcer Surface Area (USA) in cm ²					
	Post (1)	Pre	Post (2)	Pre	Post (2)	Post (1)
Mean ±SD	6.87±1.38	6.98±1.35	6.83±1.37	6.98±1.35	6.83±1.37	6.87±1.38
T. value	-5.68		-7.53		-8.90	
P. value	0.024 ^b		0.019 ^b		0.018 ^b	

SD= Standard deviation, P-value= Probability level, ^b= Significant difference.

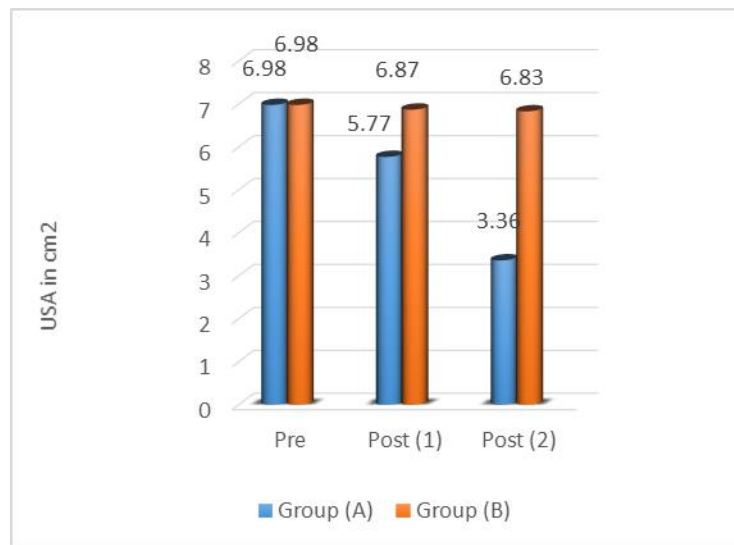


Figure (1): Showed the bars representing the mean values of ulcer surface area in cm² of the 3 records of both groups of the study.

V- Comparison between the means of the 3 records of USA in the two groups of the study.

There was non-significant differences in the first pre-treatment records of USA, between the group (A) and the group (B) ($P > 0.05$). As shown in table (4): there was a highly significant decrease in the post (2) records of USA, between group (A) and group (B) ($P < 0.05$).

Table (4): Showed the statistical analysis of the three records of the USA in cm² for the two groups of the study.

Statistics	Ulcer Surface Area (USA) in cm ²					
	Pre (Before Treatment)		Post (1) (After 4 weeks)		Post (2) (After 8 weeks)	
	Group (A) (N=20)	Group (B) (N=20)	Group (A) (N=20)	Group (B) (N=20)	Group (A) (N=20)	Group (B) (N=20)
Mean ± SD	6.98±1.36	6.98±1.36	5.77±1.56	6.87±1.38	3.36±1.3	6.83±1.37
T. value	0.1		1.45		4.44	
P. value	0.66 ^a		0.001 ^b		0.001 ^b	

SD= Standard deviation, P-value= Probability level, ^a=Non-significance, ^b= Significant difference.

VII- Results of Ankle Brachial Pressure Index (ABPI) in the group A (PEMFs group).

As observed in table (5) and figure (2), there was a highly significant increase between the means of the post (1) records (After 1 month of the treatment with PEMFs) and the pre- treatment records ($P < 0.05$). Also there was a highly significant increase between the mean of the post (2) records (After 2 months of the treatment with PEMFs) and the pre- treatment records ($P < 0.05$). As well as there was a highly significant increase between the means of the post (2) records and the post (1) records ($P < 0.05$).

Table (5): Showed the statistical analysis of the 3 records of ABPI in group (A).

Statistics	Ankle Brachial Pressure Index (ABPI)					
	Post (1)	Pre	Post (2)	Pre	Post (2)	Post (1)
Mean \pm SD	0.75 \pm 0.03	0.57 \pm 0.1	0.85 \pm 0.04	0.57 \pm 0.1	0.85 \pm 0.04	0.75 \pm 0.03
T. value	7.52		9.98		8.60	
P. value	0.0001 ^b		0.0001 ^b		0.0001 ^b	

SD= Standard deviation, P-value= Probability level, ^b= Significant difference.

VIII- Results of ABPI in the group B (Routine conventional therapy only).

As observed from table (6) and figure (2), there were significant increases between means of post (1) and pre-treatment records, between means of post (2) and pre-treatment records, as well as between means of post (2) and post (1) records ($P < 0.05$).

Table (6): Showed the statistical analysis of the 3 records of in group B (Routine conventional therapy only).

Statistics	Ankle Brachial Pressure Index (ABPI)					
	Post (1)	Pre	Post (2)	Pre	Post (2)	Post (1)
Mean \pm SD	0.59 \pm 0.1	0.57 \pm 0.1	0.62 \pm 0.1	0.57 \pm 0.1	0.62 \pm 0.1	0.59 \pm 0.1
T. value	7.76		6.28		4.09	
P. value	0.044 ^b		0.038 ^b		0.029 ^b	

SD= Standard deviation, P-value= Probability level, ^b= Significant difference.

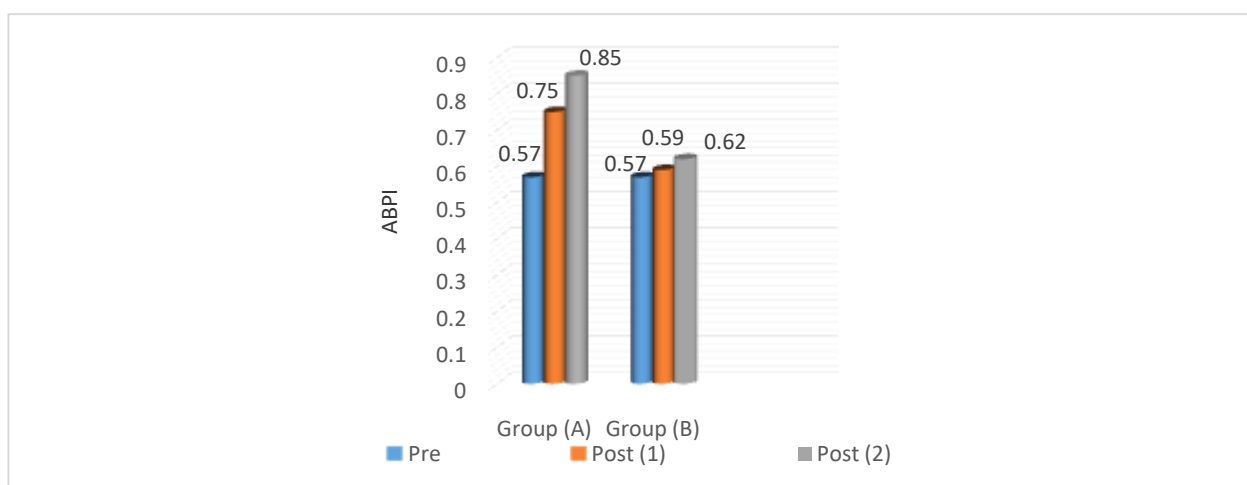


Figure (2): Showed bars representing the mean values of ABPI in the 3 records of the two groups of the study.

IX - Comparison between the means of the three records of ABPI in the two groups of the study.

As observed in table (7): There was non-significant difference in the pre-treatment records of ABPI, between both groups of the study ($P > 0.05$). Also, there was a highly significant increase in the post (1) records ($P < 0.05$). As well as there was a highly significant increase in the post (2) records, between both groups of the study ($P < 0.05$).

Table (7): Showed the statistical analysis of the three records of the ABPI in the two groups of the study.

Statistics	Ankle Brachial Pressure Index (ABPI)					
	Pre (Before treatment)		Post (1) (After 4 weeks)		Post (2) (After 8 weeks)	
	Group (A) (N=20)	Group (B) (N=20)	Group (A) (N=20)	Group (B) (N=20)	Group (A) (N=20)	Group (B) (N=20)
Mean \pm SD	0.57 \pm 0.1	0.57 \pm 0.1	0.75 \pm 0.03	0.59 \pm 0.1	0.85 \pm 0.04	0.62 \pm 0.1
T. value	0.5		1.43		4.3	
P. value	0.62 ^a		0.0001 ^b		0.0001 ^b	

SD= Standard deviation, P-value= Probability level, ^a=Non-significance, ^b= Significant difference.

X- Results of Visual Analogue Scale (VAS) in group A (PEMFs group).

As observed from table (8) and figure (3), there were a highly statistical significant ($P < 0.05$) decrease in ulcer pain after 1 month of application of treatment (Post 1) when compared with corresponding mean values of pain before treatment (Pre- treatment). Also, there were a highly statistical significant decrease ($P < 0.05$) in ulcer pain after 2 months (Post 2) when compared with corresponding mean values of pain before treatment (Pre), and after 1 month of application of treatment (Post 1), respectively.

Table (8): The statistical analysis of the three records of VAS in group A.

Statistics	Visual Analogue Scale (VAS)					
	Post (1)	Pre	Post (2)	Pre	Post (2)	Post (1)
Mean \pm SD	4 \pm 0.8	7.35 \pm 1.14	2.2 \pm 0.83	7.35 \pm 1.14	2.2 \pm 0.83	4 \pm 0.8
T-Value	20.11		26.32		15.39	
P-Value	0.001 ^b		0.001 ^b		0.001 ^b	

SD= Standard deviation, P-value= Probability level, ^b= Significant difference.

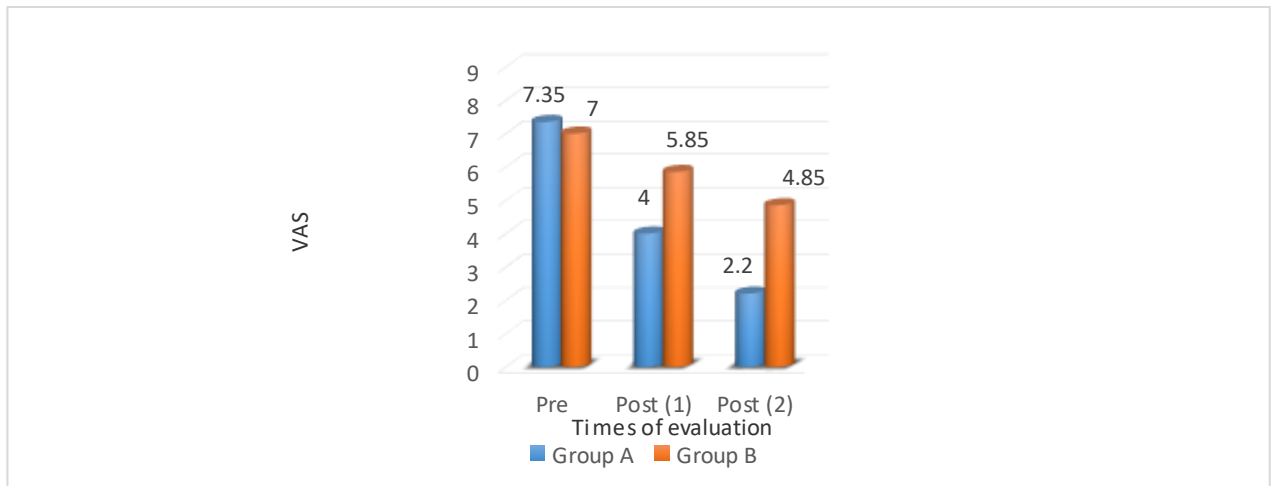
XI- Results of Visual Analogue Scale (VAS) in group B (Routine conventional therapy only).

As observed from table (9) and figure (3), there were a highly statistical significant ($P < 0.05$) decrease in venous ulcer pain after 1 month of application of treatment (Post 1) when compared with corresponding mean values of pain before treatment (Pre). Also, there were a highly statistical significant decrease ($P < 0.05$) in pain after 2 months of application of treatment (Post 2) when compared with corresponding mean values of pain before treatment (Pre), and after 1 month of application of treatment (Post 1), respectively.

Table (9): The statistical analysis of the three records of VAS in group B.

Statistics	Visual Analogue Scale (VAS)					
	Post (1)	Pre	Post (2)	Pre	Post (2)	Post (1)
Mean \pm SD	5.85 \pm 1.4	7 \pm 1.3	4.85 \pm 1.6	7 \pm 1.3	4.85 \pm 1.6	5.85 \pm 1.4
T-Value	8.76		10.30		5.63	
P-Value	0.001 ^b		0.001 ^b		0.001 ^b	

SD= Standard deviation, P-value= Probability level, ^b= Significant difference.

**Figure (3): Showed the mean values of three records of between group A& B.**

XII- Comparison between the means of the three records of VAS in the two groups of the study.

As observed from table (10), and figure (3), the statistical analysis of mean differences of VAS before treatment (Pre), after 1 month of application of treatment (Post 1), and after 2 months of application of treatment (Post 2), between both groups (A& B) revealed the following results;

There were no statistical significant differences ($P>0.05$) in mean value of VAS before treatment (Pre) between both groups (A& B). There were statistical significant differences ($P<0.05$) in VAS after 1 month of treatment application (Post 1) between both groups (A& B). Also, there were statistical significant decrease ($P<0.05$) in VAS after 2 months of treatment application (Post 2) between both groups (A& B).

Table (10): The statistical comparative analysis of the three records of Visual Analogue Scale (VAS) between the two groups of the study.

Statistics	Visual Analogue Scale (VAS)					
	Pre (Before Treatment)		Post (1) (After 4 weeks)		Post (2) (After 8 weeks)	
	Group (A) (N=20)	Group (B) (N=20)	Group (A) (N=20)	Group (B) (N=20)	Group (A) (N=20)	Group (B) (N=20)
Mean \pm SD	7.35 \pm 1.14	7 \pm 1.26	4.0 \pm 0.8	5.85 \pm 1.4	2.2 \pm 0.83	4.85 \pm 1.6
T-value	0.92		-5.18		-6.57	
P-value	0.36 ^a		0.001 ^b		0.001 ^b	

SD= Standard deviation, P-value= Probability level, ^a=Non-significance, ^b= Significant difference.

Discussion

Microcirculation is the stream of blood via the microvasculature: the arterioles, capillaries, and venules. It is these vessels that nourish the body's tissues and organs. Two vital functions of the microcirculatory system were to modify blood stream in line with the various metabolic requirements of the tissues it serves and to stabilize blood stream and pressure by making local regulatory modifications⁴²⁻⁴⁵.

In complex leg ulcer, prolonged presence of inflammatory cells, altered expression of growth factors, neuropeptides and their receptors in addition to extended activity of proteolytic enzymes are responsible for the delay within the wound healing process located in leg ulcer cases⁴⁶. By increasing the volume of blood exposed, it was expected to decrease management exposure time and/or healing time⁴⁷.

Few trials had been made to discover the parameters of microcirculation and microvasculature while tissue and/or blood vessels were exposed to a magnetic field (MF). Recently, MFs had been shown to have effective consequences on several human systems. For instance, it was documented that MF exposure can provide analgesia, lowering healing time for fractures, increase the velocity of nerve regeneration, act as a treatment for depression, and provide different clinical benefits⁴⁸⁻⁵¹. Extended knowledge of the influence of MFs on microvascular activity may have significant therapeutic capability.

An overview of epidemiological researches couldn't give a direct correlation between exposure to EMF and the occurrence of cancers⁵². EMF therapy for leg ulcer appears as a unique, non-invasive, effective and secure choice to accelerate leg ulcer healing that might be used along with different preventive and therapeutic interventions to securely reduce leg ulcer complications that lead to amputations⁵³. Additionally, the use of electromagnetic treatment does not elicit any complications from direct contact with the electrodes which are followed by different electro physical modalities. Certainly, electromagnetic therapy can be applied with the presence of casts or wound dressings, with a low risk of infection⁵⁴.

Previous studies mainly focused on wound size measurement and its closure that was found inconsistent and not reliable². In contrast, the present study comprised a comprehensive assessment on vascular ulcer healing, including the wound closure, microcirculation and pain. Therefore, this present study designed to analyze the results obtained after a period of 2 consecutive months using pulsed electromagnetic fields (PEMFs) in patients with chronic painful vascular leg ulcers. The group of patients treated with PEMFs in addition to routine conventional therapy (Group A) showed a greater reduction in pain and an improvement of healing of ulcers and microcirculation compared with the group treated with received their routine conventional alone (Group B). The comparison of wound surface area results between the two groups after 8 weeks of treatment revealed significant differences in favor of the PEMFs group (Group A) compared with group (B). Comparison between the means of the post (1) records (After 4 weeks of treatment with PEMFs) and post (2) records (After 8 weeks of treatment with PEMFs) of the USA in the two groups revealed that there was a highly significant decrease ($P > 0.05$) in the post (1) records ($5.77 \pm 1.56 \text{ cm}^2$) and post (2) records ($3.36 \pm 1.3 \text{ cm}^2$) of USA, between both groups (A& B), as the means of the post (1) and post (2) records of group (B) was $6.87 \pm 1.38 \text{ cm}^2$ and $6.83 \pm 1.37 \text{ cm}^2$ respectively.

In addition to, on comparing the ABPI values between both groups before and after the rehabilitation program, the results showed that maximum improvement appeared in the PEMFs group (Group A). Comparison between the means of the post (1) and post (2) records of ABPI in the two groups showed that there was a highly significant increase ($P > 0.05$) in the post (1) (0.75 ± 0.03), between both groups of the study (A& B). While there was a highly significant increase ($p > 0.05$) in the post (2) (0.85 ± 0.04) of ABPI, between both groups (A& B), as the means of the post (1) and post (2) records of the group (B) was 0.59 ± 0.1 and 0.62 ± 0.1 respectively.

As well as, on comparing the VAS values between both groups before and after the rehabilitation program, the results showed that maximum improvement appeared in the PEMFs group (Group A). Comparison between the means of the post (1) and post (2) records of VAS in the two groups showed that there was a highly significant increase ($P > 0.05$) in the post (1) (4.0 ± 0.8), between both groups of the study (A& B). While there was a highly significant increase ($P > 0.05$) in the post (2) (2.2 ± 0.83) of VAS, between both groups (A& B), as the means of the post (1) and post (2) records of the group (B) was 5.85 ± 1.4 and 4.85 ± 1.6 respectively.

These significant differences, between PEMF group (Group A) and the group (B), which were in the form of a highly significant decrease in the USA, ABPI and VAS, were in consistent with those observed and recorded by Bachl et al.,⁵⁵; Bao et al.,⁵⁶; Callaghan et al.,⁵⁷; Cricenti et al.,⁵⁸; David et al.,⁵⁹; El-Negmy,⁶⁰; Hedén and Pilla,⁶¹; Junger et al.,⁶²; Huo et al.,⁶³; Kwan et al.,²; Manni et al.,⁶⁴; Manni et al.,⁶⁵; Mark,⁶⁶; Markov and Colbert,⁶⁷; Ohkubo et al.,⁶⁸; Ohkubo and Okano,⁶⁹; Osman et al.,⁷⁰; Ravaghi et al.,⁷¹; Santamato et al.,⁷²; Smith et al.,⁷³; Sun et al.,¹; Valbona and Richards,⁷⁴; Vianale et al.,⁷⁵; Yuan et al.,⁷⁶.

In the present study, the improvement occurred after application of PEMF on rate of healing and microcirculation in the areas of vascular ulcer may base on and caused by several theories. As Smith et al.,⁷³ stated that, when blood stream to a tissue becomes blocked or decreased, necrosis will finally arise. Local exposure of a MF might potentially cause blood vessel relaxation and elevated blood stream. Ohkubo and Okano,⁶⁹ suggests that MF exposure influences the microcirculation and microvasculature via pushing the system to keep dynamic equilibrium via biphasic responses. This form of biphasic effect might trigger a biological system to go back to its optimum state.

Previous research confirmed that persistent dilation of arterioles can result in angiogenesis⁷⁶. Also, the increase in microcirculation can prevent the inflammation and accelerate the cellular proliferation⁵⁷, which might assisting in promoting wound healing. As the microcirculation continued to enhance in the 1-month follow-up time, this suggests that PEMF produces carryover outcomes beyond the treatment duration.

Pulsed electromagnetic field (PEMF) treatment had been shown to be useful in promoting the healing of venous leg ulcers in human beings⁷¹. As it is used for elevating permeability of the cell membrane as well as blood circulation, improving oxygen supply, elevating ATP production, enhancing healing process and also epithelialization of the injured tissues, accelerating bone healing, enhancing fibroblastic as well as osteoblastic functions, in addition to its anti-inflammatory and analgesic effect^{59, 60}.

However, the physiological mechanism of how PEMFs affect blood circulation is unclear. It was suggested that magnetic fields might induce several biological effects, with implications for the solid state principle of cellular function, principle of biologic closed electrical circuits, related-induction hypothesis, and resonance theory⁷⁴. But, there is a lack of study evidence to prove any of these hypothesized biological principles⁶⁷. Several researchers have assumed that electromagnetic fields can produce therapeutic effects on the cell membrane by changing signal transduction pathways positioned at cell membrane and cell interior of biological tissues^{55, 67, 68}.

The underlying mechanisms of EMF-induced stimulation of cell proliferation and wound healing also stay unclear. Some studies proved that characteristics of EMF signals can persuade cell differentiation or improve proliferation of cell of keratinocytes^{58, 64, 65}. Manni et al.,⁶⁴ reported that EMF at 50 Hz elevated human keratinocyte cell growth. Different research also verified that low frequency EMF significantly improved human keratinocyte proliferation^{63, 75}.

Kwan et al.,² confirmed that PEMF therapy can produce vasodilation and increase peripheral blood stream, specifically in the cutaneous capillaries of the big toe. In comparison, the patients in the control group had a decrease in capillary diameters and blood stream during the study period.

Sun et al.,¹ findings confirmed that PEMFs elicit an increase in blood stream velocity of the superficial small vein as recorded in skin above the base of the 1st metatarsal bone PEMFs increase blood stream velocity of superficial small vein. An elevation in peripheral circulation may speed up removal of metabolic wastes far from skin tissues, and accelerate the healing process of damaged tissue.

Present data confirmed that the analgesic effect of the electromagnetic field is related to both the opioid and non-opioid systems. It was indicated by the studies on rats treated with low frequency electromagnetic field. Bao et al.,⁵⁶ assumed that the electromagnetic field induces an elevation in the secretion of substance P and serotonin, that are playing a vital role in the regulation of nociceptive processes. The improved secretion of opioid peptide related to an increase in serotonin binding and analgesic effect of the electromagnetic field is associated with the level of serotonin in the brain. The level of substance P concerned with the central regulation of pain, under the effect of electromagnetic field is also increased. The substance P regulates the central neurotransmission of serotonin and β -endorphin. So, the levels of three neurotransmitters – β -endorphins, serotonin and substance P – are elevated following electromagnetic field therapy⁶⁶.

Santamato et al.,⁷² observe the effect of Frequency Rhythmic Electrical Modulation System (FREMS) in management of chronic and painful venous leg ulcers in elderly. The outcomes of this clinical trial confirmed that the therapeutic and analgesic effect of FREMS, showing additional useful effects of transcutaneous electrotherapy on chronic and painful venous leg ulcers in elderly patients.

PEMF treatment had been broadened to embody the management of postoperative pain and edema in both outpatient and home settings presenting the physician a more flexible tool for patient management⁶¹.

Junger et al.,⁶² evaluated 39 patients in a placebo-controlled study on the impact of low-frequency pulsed current on healing in chronic venous ulcers. The subjects were treated with the low-frequency pulsed or a placebo for a period of 4 months. Ulcer area was decreased in both groups, but pain reduction was higher in the treatment group.

Even though there is evidence assumed that MF exposure had effective applications for circulatory problems, not all researches support this belief. Some researchers have found no impact of MFs on blood flow^{77, 78, 79}.

Schuhfried et al.,⁸⁰ assessed the effects of PEMFs on foot microcirculation of 12 healthy peoples. They reported reduce in blood stream of microcirculation from baseline to throughout intervention, in both PEMFs group (10.7 vs. 8.8) and sham PEMFs group (11.7 vs. 8.9). Blood streams of microcirculation used to drop over time, may be due to prolonged rest that they took throughout the study time. It appears that PEMFs do not prevent effects of a prolonged rest on microcirculation.

In a study, Aziz et al.,⁸¹ evaluated the impact of electromagnetic treatment (EMT) on the healing of venous leg ulcers. The authors founded no high quality proof that electromagnetic treatment increases the rate of healing of venous leg ulcers, and more research are recommended.

In another study, Aziz et al.,⁸² assessed the impacts of EMT on the pressure ulcers healing. The results founded no strong evidence of advantage in using EMT to treat pressure ulcers.

Gupta et al.,⁸³ assessed the effect of pulsed electromagnetic field treatment (PEMF) in the healing of pressure ulcers in subjects with neurological disorders in a randomized control trial. Improvement healing of ulcers was noted. But, while comparing the groups, healing was not significant. The authors founded that no significant difference in ulcer healing was noted between PEMF therapy and placebo group in this study.

Another earlier controlled trial failed didn't a significant treatment effect of electromagnetic treatment for subjects with chronic venous ulcers, however, there was a trend toward increased healing in the treatment group⁸⁴.

Also, PEMFs did not produce any significant improvements on changes in the diameter of superficial small veins present in the skin over the base of the 1st metatarsal bone⁸⁵. Similarly, magnetic fields may reduce blood viscosity, subsequently, might increase blood flow velocity.

Eventually, after the discussion of the results and according to reports of the previous investigators in fields related to this study, it can be claimed that the application of the PEMFs program had a valuable healing effect on the painful vascular ulcers as evidenced by the highly significant improvements in USA, ABPI and VAS records in patients of painful vascular ulceration.

Study limitations

This study analysis has potential limitations, each of which indicates directions for future study. This study was limited by the following factors: Sampling selection could limit the generalization of the study's findings. Every effort was made to standardize the treatment and assessment protocols to minimize potential bias due to the lack of blinding. Also, possible errors in keeping the patient rested in between applications to avoid contamination. Physiological variation in wound healing from subject to subject. Psychological status of the patients may affect results during the conduction of the study, and finally the individual differences in the patients and their effects on the rate of healing.

Further investigation into the possible role of PEMFs on microcirculation might simultaneously investigate potential cellular markers of the PEMFs mechanism. Another recommendation would be to take

perfusion measurements during the exposure. In some experimental set-ups, it is difficult to take accurate measurements during the PEMFs exposure due to interference of signals. In a number of the studies cited in this review, perfusion measurements occur post PEMFs exposure. More measurements during exposure may provide helpful information as to when a biological effect occurs. Research involving the effects of anesthetics on blood flow and blood vessels might also be important and will add further insight into the precise mechanisms behind PEMFs exposure. It may be useful to test a PEMFs effect using different anesthetics and determine whether there are any differences in results. Future investigation might also address the potential microcirculatory effects of MRI. Finally, the use of a blinded, independent outcome assessor is highly recommended for future research.

Conclusion

In summary, this study added to the literature that the application of the PEMFs is beneficial and produces better objective improvement via its valuable healing and analgesic effect and considered as a gold therapeutic tool in the management of the chronic painful leg vascular ulcers as evidenced by the highly significant decrease in USA, the highly significant increase in ABPI and the significant difference in VAS with patients of lower limb vascular ulcers. Moreover, PEMFs safely improve the rate of healing, microcirculation and relief ulcer pain.

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