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The Clinical Efficacy of Pulsed Radio Frequency Energy on Chronic Wound Healing

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Abstract: Purpose: to investigate the efficacy of pulsed radio frequency energy as physical therapy modality in the treatment of chronic lower limb ulcers. **Methods:** Forty patients who had chronic unhealed lower limb ulcers (diabetic foot ulcer) for longer than three months participated in this study. Their ages were ranged from 40-50 years with mean value 43.99±2.843 years. The patients were selected from Egypt Railway Hospital (Department of General Surgery) in the period between May 2014 and Dec 2015. Patients who met the selection criteria were divided randomly into two equal groups, Group (A): Pulsed Radio Frequency Group received PRFE with pulse width 400 µsec, 70 pulses per second with average power of 23 w for 30 min, 3 sessions per week for 6 weeks and medical care. Group (B) (Medical Treatment Group) received medical care only. **Measurements:** Wound surface area (WSA) was assessed by Digital Camera and **ImageJ 1.47.** computer software and wound volume was assessed before treatment and after 6 weeks of treatment. **Results:** The findings of this study indicated significant decrease in WSA and wound volume after treatment in both groups A and B ($P<0.001$). There was significant difference between both groups after treatment in WSA ($p<0.001$) and wound volume ($p=0.010$) with favored results in group A **Conclusion:** Pulsed radio frequency energy for 6 weeks is an effective adjuvant therapy in treatment of chronic lower limb ulcers through accelerating wound healing, reducing wound surface area (WSA) and wound volume.
Key words: (Pulsed radio frequency energy, lower limb ulcers).

Introduction

Chronic wounds such as diabetic foot ulcers, venous ulcers, and pressure ulcers are a major source of morbidity and mortality[1].

Chronic lower extremity ulcers are a major source of morbidity and health care expenditure across the world. In the last decade, numerous advanced modalities have become available that can help expedite wound healing when standard wound care modalities are unsuccessful[2].

Chronic wounds may be due to arrest of wound healing in the state of chronic inflammation, with an imbalance between protease activity and growth factor expression. The chronic wound environment has an

overload of matrix metalloproteases (MMPs), reduced amounts of tissue inhibitors of MMPs (TIMPS), senescent and dysfunctional cells with decreased proliferative and synthetic activities, and shortages in growth factors and growth factor receptors. This situation suppresses fibroblasts proliferation, motility and protein production so that the wound remain in a chronic state[3]**.**

The cost of wound care is significant. The most important components are the costs of wound-related hospitalisation and the opportunity cost of nurse time. The 32% of patients treated in hospital accounted for 63% of total costs[4]**.**

Impaired healing is a problematic and common complication of chronic wounds. Although pulsed radiofrequency energy (PRFE) has been used in the treatment of chronic wounds with promising efficacy, its mechanism is still poorly characterized[5]**.**

Pulsed radio frequency energy stimulate cultured epidermal cells in vitro, provoking a cascade of cytokines, cyclins, growth factors, and other gene products associated with wound healing[6]**.**

PRFE improve healing of lower extremity wounds. Using PRFE for at least 4 weeks in patients with peripheral vascular disease, poor glucose control, renal disease and immune-compromise patients in treatment of diabetic foot ulcers, venous leg ulcers, Stage II - IV pressure ulcers, other types of chronic wounds give a considerable percentage of wounds improvement reached more than 50% reduction in wound surface area [7]**.**

Therefore, this study was conducted to investigate the efficacy of pulsed radio frequency energy as physical therapy modality in the treatment of chronic lower limb ulcers through reducing wound surface area (WSA) and wound volume.

Experimental

Subjects

The study was conducted on in the period between May 2014 and Dec 2015. Forty patients who had chronic unhealed lower limb ulcers (diabetic foot ulcer) for longer than three months participated in this study. Their ages were ranged from 40-50 years with mean value 43.99±2.843 years. The patients were selected from Egypt Railway Hospital (Department of General Surgery). The exclusion criteria were as follows: Patients who had severe anemia, internal fixation in the area of application, implanted cardiac rhythm devices, uncontrolled hypertension or uncontrolled cardiac patients, pregnant women and presence of a tumor or cutaneous lesion that could interfere with the procedure. All patients were given a full explanation of the treatment protocol and a written informed consent form giving agreement to participation and publication of results was signed by the patients.

Study Design

This was randomized, controlled, pre-test and post-test design study. Patients who met the selection criteria were divided randomly into two equal groups, Group (A): Pulsed Radio Frequency Group. This group included 20 patients, they received PRFE with pulse width 400 µsec, 70 pulses per second with average power of 23 w for 30 min, 3 sessions per week for 6 weeks. receive medical treatment (according to the case). Group (B) Medical Treatment Group: This group included 20 patients, they received medical treatment only (according to the case). Randomization was allocated using the numbered envelops method. Patients were blinded about which group they were allocated.

Assessment

All medical and demographic data of patients was collected and the role of physical therapy importance in improving their condition was explained.

The pre- and post-intervention assessments were the WSA assessment and Wound volume assessment. The assessment was carried out before start of treatment and after 6 weeks at the end of treatment program.

Computerised photographic WSA assessment:

By using Kodak Easy share P712 Zoom Digital Camera and **ImageJ 1.47.** computer software. A square adhesive 4 × 4 cm^2 in size with 16 square grids of 1 cm^2 each, fixed as near as possible for the wound. An ordinary digital camera (Kodak Easy share P712 Zoom) used for capturing a photograph for the wound (showing the adhesive 4x4 cm^2 square). Image J ™ free open source software will be used to analyze the photograph as following: The edges of the wound were marked and the number of pixels falling under the marked wound was calculated. The edges of the square adhesive marker were marked and the number of pixels falling under the marked square adhesive marker were calculated. Since the dimensions of the square are known (16 cm2), it was possible to derive the exact size of the marked area of the wound by dividing the size of wound by the size of the square in the photo then multiplied by the actual size of the square (16 cm^2) [8].

Wound volume assessment

Using sterilized siring and Terramycin ointment. Filing the sterilized siring of 5 cm^3 with Terramycin ointment. Then filing the wound by the kwon volume of the Terramycin ointment. It is an easy accurate method for wound volume estimation.

Treatment

Preparatory procedures

Each patient was informed about experimental process as well as the significance of study and write a consent. All equipments were checked up, calibrated and prepared before application

Procedure of PRFE Therapy Technical steps:

Group A patients received 30 min of PRFE as following.

Setting up the device parameters as following: Pulse width: 0.2 msec. Frequency 27.12 MHz., pulse frequency: 70 Hz., duty cycle: 0.5% to 10%. duration of therapy per patient was 30 mine and the energy exposure: 23 w. The device applicator placed approximated as possible to the treatment area. Then the treatment was started with no thermal effect or sensation. After the treatment time ends and patient was dismissed.

Outlines of medical care

The outlines of medical care that patients of both groups received were as following: Prevention of infection, off-loading of wound area, debridement if necessary, applying medication or dressings to the ulcer day after day and managing blood glucose and other health problems.

Statistical Analysis

Statistical analysis was conducted using SPSS for windows, version 18 (SPSS, Inc., Chicago, IL). In this study, the descriptive statistics (the mean and standard deviation) were be calculated for all patients in all groups of the study for age, weight, height, BMI, WSA and wound volume variables. Comparisons between mean values of WSA and wound volume in both groups pre-treatment and post-treatment was made by independent t-test. Paired t- test was used to compare mean values of WSA and wound volume before and after treatment in the same group. P-value ≤ 0.05 was considered statistically significant.

Results

Baseline and demographic data

There were no statistically significant differences ($P>0.05$) between patients in both groups concerning age, weight, height, and BMI (Table 1). There were also no statistically significant differences between groups for any outcome variables at baseline (pre-intervention).

Table (1):General characteristics of all patient

	Mean± SD		t-value	p-value
	Group (A)	Group (B)		
Age (years)	43.74±2.759	44.23±2.974	-0.540	0.592
Height (c.m)	172±2.92	173.05±5.7	0.7332	0.468
Weight (k.g)	83.65±7.17	83.8±7.25	0.0658	0.948
BMI	28.28±1.8	27.99±1.54	0.5475	0.587

* : significant difference

Wound surface area (WSA):

As indicated at table (2) and illustrated at figure (1) "Paired t test" revealed that there was a significant reduction of WSA (t-value= 9.923, P-value =0.000*) in group A. In addition, "Paired t test" revealed that there was significant reduction in WSA (t-value= 5.226, P-value =0.000*) in group B. Unpaired t test revealed that the mean values of the "pre" treatment between both groups showed there was no significant differences (t-value= -0.011, P=0.991). Comparison between the mean values of the "post" treatment mean values in both groups showed there was significant difference of WSA (t-value= -4.389, p=0.000*) with better improvement in Group A. More over figure 2 shows complete healing of diabetic foot wound after 6 weeks of treatment application.

Table (2): Wound surface area pre and post treatment comparison in both groups and between groups pre and post treatment.:

WSA	Before treatment	After treatment	t_p value	P-value
	Mean± SD	Mean± SD		
Group A	12.60±6.36	4.69±3.57	9.923	0.000*
Group B	12.62±5.74	10.54±4.78	5.226	0.000048*
t_p value	-0.011	-4.389		
P-value	0.991	0.000088*		

SD: Standard Deviation	tp: paired t-test	
* = Significant	N.S. = non-significant	

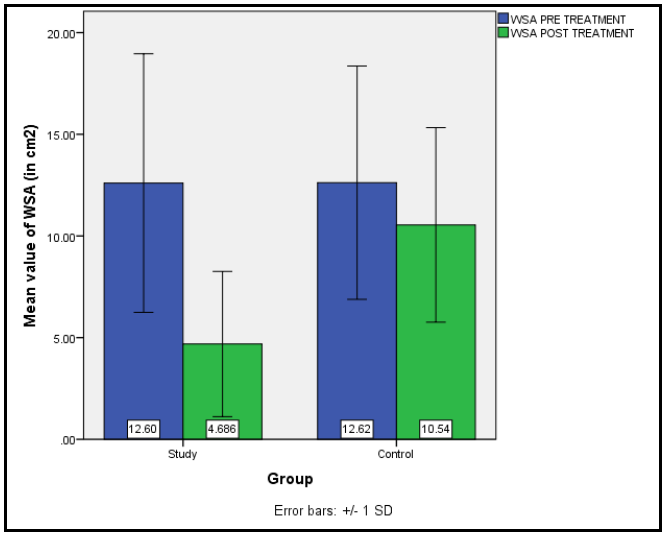

Figure. (1): Mean ±SD values of WSA of pre and post treatment in both groups.

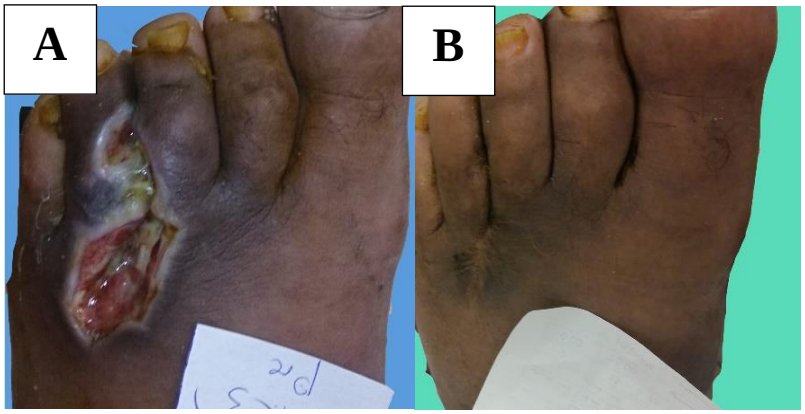

Figure (2): Diabetic ulcer in the left foot (A) before treatment and (B) after 6 weeks of PEMF treatment and medical care.

Wound volume:

As indicated at table (3) and illustrated at figure (3) "Paired t test" revealed that there was a significant reduction of Wound Volume (t-value= 7.530, P-value =0.000*) in group A (Figure 3). In addition, "Paired t test" revealed that there was significant reduction in Wound Volume (t-value= 5.748, P-value =0.000*) in group B. Unpaired t test revealed that the mean values of the "pre" treatment between both groups showed there was no significant differences (t-value= 0.719, P=0.477). Comparison between the mean values of the "post" treatment mean values in both groups showed there was significant difference of Wound Volume (t-value= -2.707, p=0.010*) with better improvement in Group A.

Table (3): Wound Volume pre and post treatment comparison in both and between groups pre and post treatment.

Wound Volume	**Before treatment**	**After treatment**	**t_p value**	**P-value**
	Mean± SD	**Mean± SD**		
Group A	5.2850±3.19741	1.6400±1.34101	7.530	0.000*
Group B	4.6150±2.67587	3.1800±2.16226	5.748	0.000015*
t_p value	0.719	-2.707		
P-value	0.477	0.010*		
SD: Standard Deviation		tp: paired t-test		
* = Significant		N.S. = non-significant		

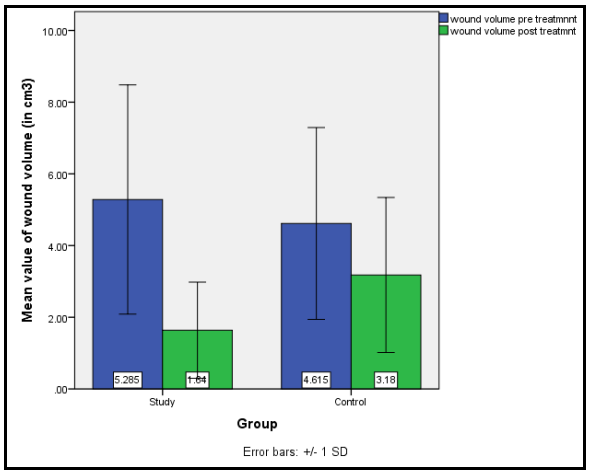

Figure. (3): Mean ±SD values of Wound Volume of pre and post treatment in both groups.

Discussion

This study investigated the efficacy of pulsed radio frequency energy as physical therapy modality in the treatment of chronic lower limb ulcers through reducing wound surface area (WSA) and wound volume.

The findings of this study indicated significant decrease in WSA after treatment in both groups A and B (P=0.000) with bitter percentage of improvement in group A (62.78%) vs (16.48% in group B). Also, there was significant difference between Group A, and Group B post treatment values of WSA (p=0.000) with favored results in group A.

Regarding the results of wound volume, both groups A and B show significant decrease in wound volume after treatment (p=0.000) with percentage of improvement 68.96%in group A and 31.09% in group B. Also, there was significant difference between Group A, and Group B post treatment values of wound volume (p=0.010) with favored results in group A.

The results of this study came in accordance with Kao et. al., who evaluate the effect of Pulsed radiofrequency energy diabetic wounded Db/db mice. Gross closure, cell proliferation, and morphometric analysis of CD31-stained wound cross-sections were assessed. The mRNA expression of profibrotic factors (transforming growth factor-β and platelet-derived growth factor-A), angiogenetic factors (vascular endothelial growth factor and basic fibroblast growth factor), and extracellular matrix components (collagen I and α-smooth muscle actin) were evaluated by quantitative reverse-transcriptase polymerase chain reaction. Collagen protein level of the wound was determined by Western blot analysis. Cell migration was monitored in monolayer dermal fibroblast cultures. The degree of collagen alignment and gelation time was quantitatively assessed using image analysis techniques. Results show that pulsed radiofrequency energy-treated wounds were characterized by dermal cell proliferation and increased collagen synthesis [9].

The result of this study came in accordance with Maier, who evaluate the effect of PEMF on two patients with painful chronic cutaneous wounds in the lower limb. Adjunctive pulsed radio frequency energy was administered for 30 minutes twice daily through an applicator pad placed directly on the dressing over the wound area. Both patients reported immediate, marked pain reduction, allowing compression therapy. The ulcers healed completely within 3 weeks for patient 1 and 28 weeks for patient 2 [10].

The result of the current study supported by Kloth et. al., who studied the effect of PRF treatment on healing of pressure ulcers in spinal cord injured patient. The study concluded that PRF treatment is a cost saving intervention that can stimulate the endogenous bioelectric tissue repair processes when wounds do not show evidence of healing with standard wound treatment. In addition, acceleration of tissue healing also reduces the pain and suffering experienced by individuals afflicted with chronic wounds. Also accelerated healing of chronic wounds with PRF enabled patients to return to functional activities sooner so undesirable complications do not develop [11].

In agreement with this study Bentall, who evaluated the effect of pulsed radio-frequency energy in treatment of skin wounds. Resultes show that PEMF influenced the processes of acute secondary wound healing. The rate of healing was accelerated and the histological appearance of the actively treated wounds showed that the healed epidermis was more like normal skin than the scar tissue typical of secondary wound healing [12].

The beneficial effect of PRFE in treatment of lower limb ulcers is due to improvement in the expression of genes involved in angiogenesis and wound remodeling. The expression of genes involved in angiogenesis and wound remodeling was assessed using microarray analysis of cultured human dermal fibroblasts (HDF) and human epidermal keratinocytes (HEK). Relative transcript levels of factors involved in these processes were determined at multiple time points following PRFE treatment using cDNA microarray analysis and confirmed by RT-PCR [13].

In another study conducted by Moffett et. al., supports a mechanism whereby PRFE field treatment promotes the healing of chronic wounds and facilitating the transition from a chronic inflammation cycle to that of a functional wound healing cycle, a process that in part may involve PRFE-mediated immunomodulation. The study concluded that PRFE field treatment of human dermal fibroblasts and epidermal keratinocytes resulted in robust increases in the levels of numerous transcripts encoding factors such as matrix metalloproteinases (MMPs) and their inhibitors (TIMPs), interleukin (IL)-related genes, interferon (INF)-

related genes, and tumor necrosis factor (TNF)-related genes, that involved in the inflammatory phase of the wound healing process [14].

Also, PEMF modulates the rate of calmodulin (CaM) activation when intracellular Ca2+ increases after insult or injury. This, in turn, modulates the activation of Ca/CaM-dependent constitutive nitric oxide synthase (cNOS) and, therefore, the dynamics of nitric oxide (NO) in the target cells/tissues. The Ca/CaM-dependent NO cascade is an important and early response to physical, chemical or thermal injury [15].

Conclusion

The results of current study showed that pulsed radio frequency energy for 6 weeks is an effective adjuvant therapy in treatment of chronic lower limb ulcers through accelerating wound healing, reducing wound surface area (WSA) and wound volume.

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