Evaluation of the Effect of Pulsed Electromagnetic Field Therapy in the Treatment of Chronic Wounds

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ABSTRACT

Background: *Recent innovations, such as hydrosurgery (Versajet), ultrasound therapy (the MIST therapy device), and plasma-mediated bipolar radio-frequency ablation therapy (Coblation) could represent an alternative to conventional debridement in many cases, especially for chronic non-healing wounds. Pulsed electromagnetic field (PEMF) has been used clinically as an intervention to enhance healing of chronic ulcers.* ***Objective:*** *To evaluate the effect of pulsed electromagnetic field therapy on healing of chronic wounds, as regard timing and quality of healing.* ***Patients and Methods:*** *Prospective study of the results 50 cases with different types of chronic wounds, according to inclusion and exclusion criteria, the patients' age ranged from 20 -70 years. Selected from outpatient clinic of military hospital, or transferred through civilian outpatient's clinic in different hospitals and specific diabetic foot centers. They are diagnosed as infected resistant chronic wounds depending on clinical, laboratory and radiological investigations due to various reasons from August 2018 until March 2019, and managed by pulsed EMF therapy.* ***Results:*** *The analysis showed that there were statistically significant associations between treatment outcomes and pain (p =0.018), edema (p =0.005), number of sessions (p <0.001), microbial eradication (p =0.008). On the other hand, we found that there were statistically significant associations between complication rates and treatment outcome (p =0.008), microbial eradication (p <0.001), and hospital stay (p =0.002).* ***(Table 5-15). Conclusion:*** *the PEMF therapy is safe and effective treatment option for patients with chronic, resistant wounds. The current study shows that the PEFM achieved high success rate with few complications. In addition, our analysis showed that achieving complete closure of the wound can be associated significant symptomatic relief and few incidence of complications. Nevertheless, further studies are still needed to confirm our findings.*

Keywords: *Chronic, Pulsed, healing, ulcer*

INTRODUCTION

A wound can be described as a defect or a break in the skin, resulting from physical or thermal damage or as a result of the presence of an underlying medical or physiological condition. According to the Wound Healing Society, a wound is the result of 'disruption of normal anatomic structure and function **(1).**

Wound healing is a dynamic process consisting of three continuous, overlapping, and precisely programmed phases. The events of each phase must happen in a precise and regulated manner. Interruptions, aberrancies, or prolongation in the process can lead to delayed wound healing or a non-healing chronic wound **(2).**

In adult humans, optimal wound healing involves the following the events: 1- rapid hemostasis; 2- appropriate inflammation; 3- mesenchymal cell differentiation, proliferation, and migration to the wound site; 4- suitable angiogenesis; 5- prompt re-epithelialization (regrowth of epithelial tissue over the wound surface); and 6- proper synthesis, cross-linking, and alignment of collagen to provide strength to the healing tissue **(2). (Fig 1).**

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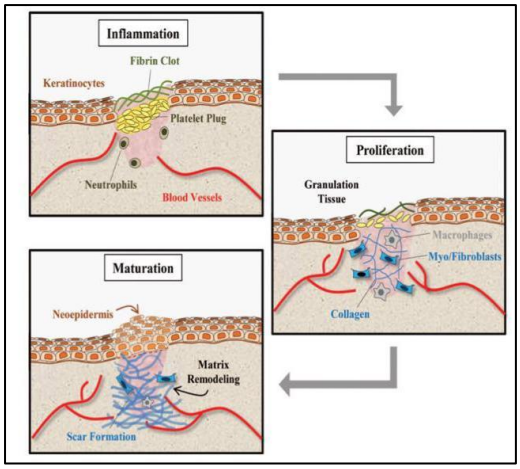

Fig 1: the three classic stages of wound repair

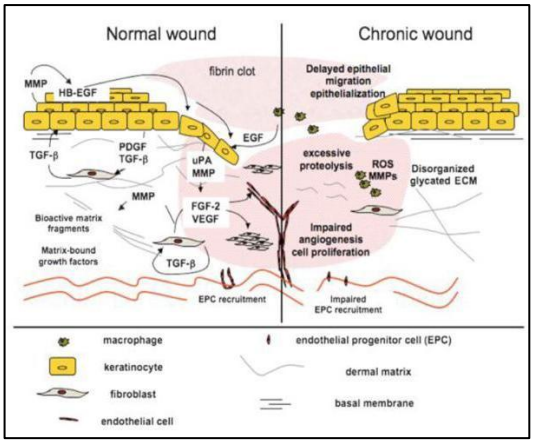

Fig. 2: Normal versus chronic wound healing

Wounds that exhibit impaired healing, including delayed acute wounds and chronic wounds, generally have failed to progress through the normal stages of healing. Such wounds frequently enter a state of pathologic inflammation due to a postponed, incomplete, or uncoordinated healing process [(3)]**. (Fig 2).**

Multiple factors can lead to impaired wound healing. In general terms, the factors that influence repair can be categorized into; A- Local factors (as oxygenation, infection, foreign body, and necrosis) are those that directly influence the characteristics of the wound itself [(4)]**,** B- systemic factors (as nutrition, age and gender, sex hormones, stress, ischemia), diseases (as diabetes, jaundice, uremia), obesity, medications (as glucocorticoid steroids and non-steroidal anti-inflammatory drugs), chemotherapy, alcoholism, smoking and Immunocompromised conditions(as cancer and radiation therapy) are the overall health or disease state of the individual that affect his or her ability to heal. Many of these factors are related, and the systemic factors act through the local effects affecting wound healing [(4)]**.**

The vast majority of chronic wounds can be classified into three categories: vascular ulcers (eg, venous and arterial ulcers), diabetic ulcers and pressure ulcers. Some common features shared by each of these include a prolonged or excessive inflammatory phase, persistent infections, formation of drug-resistant microbial biofilms and the inability of dermal and/or epidermal cells to respond to reparative stimuli [(5)]**.**

As regards laboratory investigations culture and sensitivity swabbing for the discharging wounds with drug-resistant microbial biofilms. Diagnostic biopsy should be considered from an ulcer lesion under the following conditions: a) An ulcer in which the clinical diagnosis not established or to confirm diagnosis,b) A non-healing ulcer that does not heal within three to four months of optimal treatment, c) Suspected malignancy [(6)]**.**

Correctly identifying the etiology of a chronic wound as well as the local and systemic factors that may be contributing to poor wound healing is the key to successful wound treatment [(7)]**.**

Novel approaches in managing this type of wounds is Pulsed electromagnetic field (PEMF) technologies that have shown usefulness as adjunctive therapy for the treatment of chronic wounds. These relatively simple devices use an external, non-invasive PEMF to generate short bursts of electrical current in injured tissue without producing heat or interfering with nerve or muscle function. Recently, increased understanding of the mechanism of action of PEMF therapy has permitted technologic advances yielding economical and disposable PEMF devices. With these devices, PEMF therapy has been broadened to include the treatment of postoperative pain and edema in both outpatient and home settings, offering the physician a more versatile tool for patient management [(8)].

AIM OF THE WORK

The present work aims to evaluate the effect of pulsed electromagnetic field therapy on healing of chronic wounds, as regard timing and quality of healing.

PATIENTS AND METHODS

Prospective study of the results 50 cases with different types of chronic wounds, according to inclusion and exclusion criteria, the patients' age ranged from 20 -70 years. Selected from outpatient clinic of military hospitals or transferred through civilian outpatient's clinics in different hospitals and specific diabetic foot centers. They are diagnosed as infected resistant chronic wounds depending on clinical, laboratory and radiological investigations due to various reasons from August 2018 until March 2019, and managed by pulsed EMF therapy.

Inclusion Criteria:

All male and female patients reported as chronic wounds or ulcers (Diabetic ulcers- Decubitus ulcers) Large wound defect (post-operative- post traumatic)- Infectious disease, wounds with massive exudate / transudate, were admitted to hospital. The diagnosis of chronic wounds based on a combination of a compatible history – examination and investigation. Informed written consent was obtained from the patients, which includes compliance with the requirements and restrictions listed in the consent form. Male and female patients ≥ 20 years of age Patients agreed to use a medically acceptable physical contraceptive barrier method during the treatment phase. Body mass index less than 30 kg/m^2 **(Table 1)**.

Exclusion Criteria:

Pregnancy and breast feeding, hemodynamic instability, history of having Aneurysm clip(s), any metallic fragment or foreign body, Coronary and peripheral artery stents, Aortic stent graft, Prosthetic heart valves and annuloplasty rings, Cardiac occluder devices, Vena caval filters and embolization coils, Haemodynamic monitoring and temporary pacing devices, eg, Swan–Ganz catheter, Haemodynamic support devices, Cardiac pacemaker, Implanted cardioverter-defibrillator (ICD), Retained transvenous pacemaker and defibrillator leads, Electronic implant or device, eg, insulin pump or other infusion pump, Cochlear, otologic, or other ear implant, Neurostimulation system, Shunt (spinal or intraventricular), Joint replacement (eg, hip, knee, etc), Any type of metallic prosthesis (eg, eye, penile, etc), Body piercing jewellery and Hearing aid. Patients exhibits signs of sepsis: Shock or profound hypotension, defined as systolic blood pressure <90 mm Hg or a decrease of >40 mm Hg from baseline that is not responsive to fluid challenge; Hypothermia (core temperature <35.6°C or <96.1°F); Disseminated intravascular coagulation as evidenced by prothrombin time (PT) or activated partial thromboplastin time (aPTT) 2 times the upper limit of normal, ischemic ulcers due to peripheral vascular diseases, third-degree burn or a burn covering more than 9% of the total body surface area, presence of necrotizing fasciitis. Mentally or neurologically disabled patients that are considered not fit to approve their participation in the study. Refusal to give informed consent. Patients who had participated in another research study involving an investigational product in the past 12 weeks. Suspicious ulcers; cancerous or precancerous lesions Necrotic tissue with eschar present in the wound without debridement . Morbid obesity Patients with age below 20 or above 70.

Informed Consent: A written informed consent was obtained from each patient before he/she got enrolled into the study.

Ethical principles: This Clinical Trial was conducted in accordance with the principles laid

down by the 18th World Medical Association ***(Helsinki, 1964)*** and all applicable amendments laid down by the World Medical Association and ICH guidelines for Good Clinical Practice.

Laws and regulations: This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of Egypt in which the Clinical Trial is performed, as well as any applicable guidelines.

Statistical analysis: Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) Statistical Package for the Social Sciences software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance;. Differences between frequencies (qualitative variables) and percentages in groups were compared by Chi-square test., multiple group by ANOVA,. ROC curve for cut off, Kappa agreement to test the agreement. P value was set at <0.05 for significant results & <0.001 for high significant result.

RESULTS

Table (1): Sex, age and BMI distribution among study groups.

		No. = 50
Sex	Females	16 (32.0%)
	Males	34 (68.0%)
Age	Mean±SD	50.34 ± 11.08
	Range	21 – 68
BMI	Underweight	15 (30.0%)
	Healthy weight	17 (34.0%)
	Overweight	18 (36.0%)

Table (2): Pre-procedure Data of the Patients.

Pre-procedure data		**Total no. = 50**
		No. (%)
Co-existing illness	None	18 (36.0%)
	DM	27 (54.0%)
	Bedridden	5 (10.0%)
Wound type	D. foot ulcer	27 (54.0%)
	Traumatic ulcer	8 16.0%)
	Decubitus ulcer	5 (10.0%)
	Post operative wound	10 (20.0%)
Organisms	Single	41 (82.0%)
	Mixed	9 (18.0%)
Organism type	Proteus	6 (12.0%)
	Staph aureus	20 (40.0%)
	Psudomonus A.	10 (20.0%)
	E.coli	13 (26.0%)
	Strept group a	10 (20.0%)

Table (3): Pre-procedure Therapy.

		Total no. = 50
		No. (%)
Resistance	No resistance	27 (54.0%)
	MDR	23 (46.0%)
Adjuvant treatment	None	17 (34.0%)
	Antibiotics	27 (54.0%)
	VAC therapy	6 (12.0%)

Table (4): Procedure Data of the Included Patients.

Procedure data		**Total no. = 50**
		No. (%)
Pain	Not improved	15 (30.0%)
	Improved	33 (66.0%)
	Increased	2 (4.0%)
Hyperemia	None	23 (46.0%)
	Increased	27 (54.0%)
Edema	None	17 (34.0%)
	Reduced	33 (66.0%)
Number of sessions	< 12	20 (40.0%)
	(12 - 24)	22 (44.0%)
	> 24	8 (16.0%)
Duration of treatment	< 6 weeks	15 (30.0%)
	(6 - 12)	29 (58.0%)
	> 12 weeks	6 (12.0%)
Treatment Outcome	No Closure	1 (2.0%)
	Partial Closure	10 (20.0%)
	Complete Closure	39 (78.0%)
Microbial eradication	No	4 (8.0%)
	Yes	46 (92.0%)
Complications	Not complicated	43 (86.0%)
	Complicated	7 (14.0%)
Type of complications	Oozing	3 (42.9%)
	Persistant infection	4 (57.1%)
Hospital stay	No	45 (90.0%)
	Yes	5 (10.0%)

Table (5): Associations between treatment outcomes and pre-procedure data.

Pre-procedure data		**Treatment Outcome**		**Chi-square test**		
		Partial Closure	**Complete Closure**	**X^2**	**P-value**	**Sig.**
		No. (%)	**No. (%)**			
Co-existing illness	None	4 (40.0%)	14 (35.9%)	1.622	0.444	NS
	DM	4 (40.0%)	22 (56.4%)			
	Bedridden	2 (20.0%)	3 (7.7%)			
Wound type	D. foot ulcer	4 (40.0%)	22 (56.4%)	1.690	0.639	NS
	Traumatic ulcer	2 (20.0%)	6 (15.4%)			
	Decubitus ulcer	2 (20.0%)	3 (7.7%)			
	Post operative wound	2 (20.0%)	8 (20.5%)			
Organisms	Single	9 (90.0%)	31 (79.5%)	.639a	0.444	NS
	Mixed	1 (10.0%)	8 (20.5%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (6): Associations between treatment outcomes and type of organism or resistance.

		Treatment Outcome		Chi-square test		
		Partial Closure	Complete Closure	X^2	P-value	Sig.
		No. (%)	No. (%)			
Proteus	Negative	8 (80.0%)	35 (89.7%)	0.703	0.402	NS
	Positive	2 (20.0%)	4 (10.3%)			
Staph aureus	Negative	8 (80.0%)	22 (56.4%)	1.866	0.172	NS
	Positive	2 (20.0%)	17 (43.6%)			
Psudomonus A.	Negative	9 (90.0%)	30 (76.9%)	0.838	0.360	NS
	Positive	1 (10.0%)	9 (23.1%)			
E.coli	Negative	8 (80.0%)	28 (71.8%)	0.275	0.600	NS
	Positive	2 (20.0%)	11 (28.2%)			
Strept group a	Negative	6 (60.0%)	33 (84.6%)	2.969	0.085	NS
	Positive	4 (40.0%)	6 (15.4%)			
Resistance	No resistance	3 (30.0%)	24 (61.5%)	3.200	0.074	NS
	MDR	7 (70.0%)	15 (38.5%)			
Adjuvant treatment	None	4 (40.0%)	12 (30.8%)	4.879	0.087	NS
	Antibiotics	3 (30.0%)	24 (61.5%)			
	VAC therapy	3 (30.0%)	3 (7.7%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (7): Associations between treatment outcomes and procedure data.

Procedure data		Treatment Outcome		Chi-square test		
		Partial Closure	Complete Closure	X^2	P-value	Sig.
		No. (%)	No. (%)			
Pain	Not improved	6 (60.0%)	8 (20.5%)	8.024	0.018	S
	Improved	3 (30.0%)	30 (76.9%)			
	Increased	1 (10.0%)	1 (2.6%)			
Hyperemia	None	4 (40.0%)	18 (46.2%)	0.122	0.727	NS
	Increased	6 (60.0%)	21 (53.8%)			
Edema	None	7 (70.0%)	9 (23.1%)	7.969	0.005	HS
	Reduced	3 (30.0%)	30 (76.9%)			
Number of sessions	< 12	2 (20.0%)	18 (46.2%)	17.544	0.000	HS
	(12 - 24)	2 (20.0%)	19 (48.7%)			
	> 24	6 (60.0%)	2 (5.1%)			
Duration of treatment	< 6 weeks	1 (10.0%)	14 (35.9%)	9.760	0.008	HS
	(6 - 12)	5 (50.0%)	23 (59.0%)			
	> 12 weeks	4 (40.0%)	2 (5.1%)			
Microbial eradication	No	3 (30.0%)	0 (0.0%)	12.463	0.000	HS
	Yes	7 (70.0%)	39 (100.0%)			
Complications	Not complicated	7 (70.0%)	36 (92.3%)	3.686	0.055	NS
	Complicated	3 (30.0%)	3 (7.7%)			
Type of complications	Oozing	0 (0.0%)	3 (100.0%)	6.000	0.014	S
	Persistant infection	3 (100.0%)	0 (0.0%)			
Hospital stay	No	10 (100.0%)	34 (87.2%)	1.428	0.232	NS
	Yes	0 (0.0%)	5 (12.8%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (8): Associations between complications rate and pre-procedure data.

		Complications		Chi-square test		
		Not complicated	Complicated	X^2	P-value	Sig.
		No. (%)	No. (%)			
Co-existing illness	None	15 (34.9%)	3 (42.9%)	0.935	0.627	NS
	DM	23 (53.5%)	4 (57.1%)			
	Bedridden	5 (11.6%)	0 (0.0%)			
Wound type	D. foot ulcer	23 (53.5%)	4 (57.1%)	1.143	0.767	NS
	Traumatic ulcer	7 (16.3%)	1 (14.3%)			
	Decubitus ulcer	5 (11.6%)	0 (0.0%)			
	Post operative wound	8 (18.6%)	2 (28.6%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (9): Associations between complications rate and type of organism.

		Complications		Chi-square test		
		Not complicated	Complicated	X^2	P-value	Sig.
		No. (%)	No. (%)			
Organisms	Single	35 (81.4%)	6 (85.7%)	0.076	0.783	NS
	Mixed	8 (18.6%)	1 (14.3%)			
Proteus	Negative	38 (88.4%)	6 (85.7%)	0.040	0.841	NS
	Positive	5 (11.6%)	1 (14.3%)			
Staph aureus	Negative	26 (60.5%)	4 (57.1%)	0.028	0.868	NS
	Positive	17 (39.5%)	3 (42.9%)			
Psudomonus A.	Negative	34 (79.1%)	6 (85.7%)	0.166	0.684	NS
	Positive	9 (20.9%)	1 (14.3%)			
E.coli	Negative	31 (72.1%)	6 (85.7%)	0.581	0.446	NS
	Positive	12 (27.9%)	1 (14.3%)			
Strept group a	Negative	35 (81.4%)	5 (71.4%)	0.374	0.541	NS
	Positive	8 (18.6%)	2 (28.6%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (10): Associations between complications rate and resistance.

		Complications		Chi-square test		
		Not complicated	Complicated	X^2	P-value	Sig.
		No. (%)	No. (%)			
Resistance	No resistance	25 (58.1%)	2 (28.6%)	2.119	0.145	NS
	MDR	18 (41.9%)	5 (71.4%)			
Adjuvant treatment	None	14 (32.6%)	3 (42.9%)	3.025	0.220	NS
	Antibiotics	25 (58.1%)	2 (28.6%)			
	VAC therapy	4 (9.3%)	2 (28.6%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (11): Associations between complications rate and procedure data.

		Complications		**Chi-square test**		
		Not complicated	**Complicated**	**X^2**	**P-value**	**Sig.**
		No. (%)	**No. (%)**			
Pain	Not improved	11 (25.6%)	4 (57.1%)	2.985	0.225	NS
	Improved	30 (69.8%)	3 (42.9%)			
	Increased	2 (4.7%)	0 (0.0%)			
Hyperemia	None	19 (44.2%)	4 (57.1%)	0.407	0.524	NS
	Increased	24 (55.8%)	3 (42.9%)			
Edema	None	13 (30.2%)	4 (57.1%)	1.943	0.163	NS
	Reduced	30 (69.8%)	3 (42.9%)			
Number of sessions	< 12	20 (46.5%)	0 (0.0%)	5.452	0.065	NS
	(12 - 24)	17 (39.5%)	5 (71.4%)			
	> 24	6 (14.0%)	2 (28.6%)			
Duration of treatment	< 6 weeks	13 (30.2%)	2 (28.6%)	0.042	0.979	NS
	(6 - 12)	25 (58.1%)	4 (57.1%)			
	> 12 weeks	5 (11.6%)	1 (14.3%)			
Treatment Outcome	No Closure	0 (0.0%)	1 (14.3%)	9.558	0.008	HS
	Partial Closure	7 (16.3%)	3 (42.9%)			
	Complete Closure	36 (83.7%)	3 (42.9%)			
Microbial eradication	No	0 (0.0%)	4 (57.1%)	26.708	0.000	HS
	Yes	43 (100.0%)	3 (42.9%)			
Hospital stay	No	41 (95.3%)	4 (57.1%)	9.764	0.002	HS
	Yes	2 (4.7%)	3 (42.9%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (12): Association between hospital stay and pre-procedure data.

		Hospital stay		**Chi-square test**		
		No	**Yes**	**X^2**	**P-value**	**Sig.**
		No. (%)	**No. (%)**			
Co-existing illness	None	16 (35.6%)	2 (40.0%)	6.214	0.045	S
	DM	26 (57.8%)	1 (20.0%)			
	Bedridden	3 (6.7%)	2 (40.0%)			
Wound type	D. foot ulcer	26 (57.8%)	1 (20.0%)	8.189	0.042	S
	Traumatic ulcer	8 (17.8%)	0 (0.0%)			
	Decubitus ulcer	3 (6.7%)	2 (40.0%)			
	Post operative wound	8 (17.8%)	2 (40.0%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (13): Association between hospital stay and type of organism.

		Hospital stay		Chi-square test		
		No	Yes	X^2	P-value	Sig.
		No. (%)	No. (%)			
Organisms	Single	38 (84.4%)	3 (60.0%)	1.822	0.177	NS
	Mixed	7 (15.6%)	2 (40.0%)			
Proteus	Negative	39 (86.7%)	5 (100.0%)	0.758	0.384	NS
	Positive	6 (13.3%)	0 (0.0%)			
Staph aureus	Negative	28 (62.2%)	2 (40.0%)	0.926	0.336	NS
	Positive	17 (37.8%)	3 (60.0%)			
Psudomonus A.	Negative	37 (82.2%)	3 (60.0%)	1.389	0.239	NS
	Positive	8 (17.8%)	2 (40.0%)			
E.coli	Negative	33 (73.3%)	4 (80.0%)	0.104	0.747	NS
	Positive	12 (26.7%)	1 (20.0%)			
Strept group a	Negative	36 (80.0%)	4 (80.0%)	0.000	1.000	NS
	Positive	9 (20.0%)	1 (20.0%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (14): Association between hospital stay and resistance.

		Hospital stay		Chi-square test		
		No	Yes	X^2	P-value	Sig.
		No. (%)	No. (%)			
Resistance	No resistance	23 (51.1%)	4 (80.0%)	1.512	0.219	NS
	MDR	22 (48.9%)	1 (20.0%)			
Adjuvant treatment	None	17 (37.8%)	0 (0.0%)	2.881	0.237	NS
	Antibiotics	23 (51.1%)	4 (80.0%)			
	VAC therapy	5 (11.1%)	1 (20.0%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (15): Association between hospital stay and procedure data.

		Hospital stay		Chi-square test		
		No	Yes	X^2	P-value	Sig.
		No. (%)	No. (%)			
Pain	Not improved	13 (28.9%)	2 (40.0%)	0.438	0.803	NS
	Improved	30 (66.7%)	3 (60.0%)			
	Increased	2 (4.4%)	0 (0.0%)			
Hyperemia	None	19 (42.2%)	4 (80.0%)	2.585	0.108	NS
	Increased	26 (57.8%)	1 (20.0%)			
Edema	None	15 (33.3%)	2 (40.0%)	0.089	0.765	NS
	Reduced	30 (66.7%)	3 (60.0%)			
Number of sessions	< 12	20 (44.4%)	0 (0.0%)	7.071	0.029	S
	(12 - 24)	17 (37.8%)	5 (100.0%)			
	> 24	8 (17.8%)	0 (0.0%)			
Duration of treatment	< 6 weeks	14 (31.1%)	1 (20.0%)	1.315	0.518	NS
	(6 - 12)	25 (55.6%)	4 (80.0%)			
	> 12 weeks	6 (13.3%)	0 (0.0%)			
Treatment Outcome	No Closure	1 (2.2%)	0 (0.0%)	1.567	0.457	NS
	Partial Closure	10 (22.2%)	0 (0.0%)			
	Complete Closure	34 (75.6%)	5 (100.0%)			
Microbial eradication	No	4 (8.9%)	0 (0.0%)	0.483	0.487	NS
	Yes	41 (91.1%)	5 (100.0%)			
Complications	Not complicated	41 (91.1%)	2 (40.0%)	9.764	0.002	HS
	Complicated	4 (8.9%)	3 (60.0%)			
Type of complications	Oozing	0 (0.0%)	3 (100.0%)	7.000	0.008	HS
	Persistant infection	4 (100.0%)	0 (0.0%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

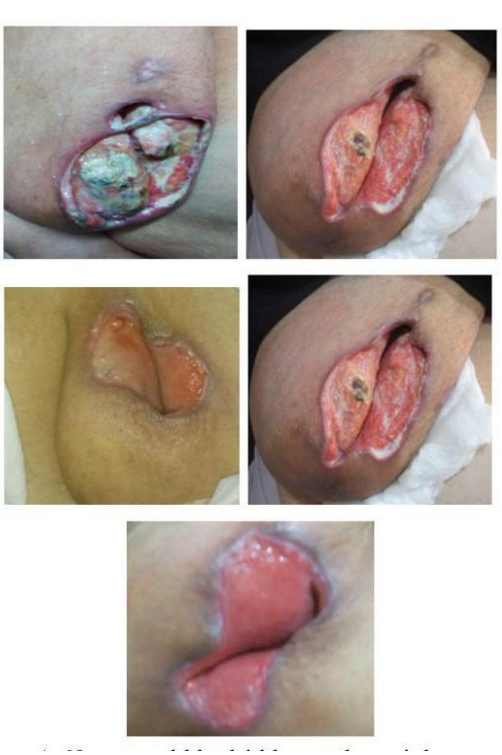

Fig 3: decubitus ulcer in gluteal region after PEMF 26 sessions

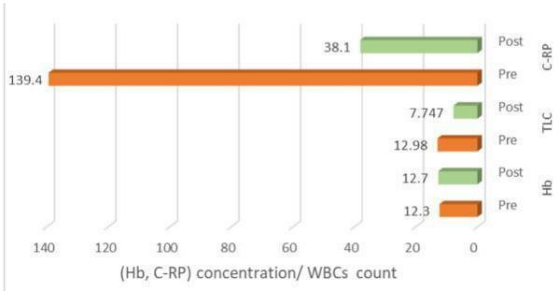

Fig 4: Association between Hb, TLC and C-RP pre and post sessions.

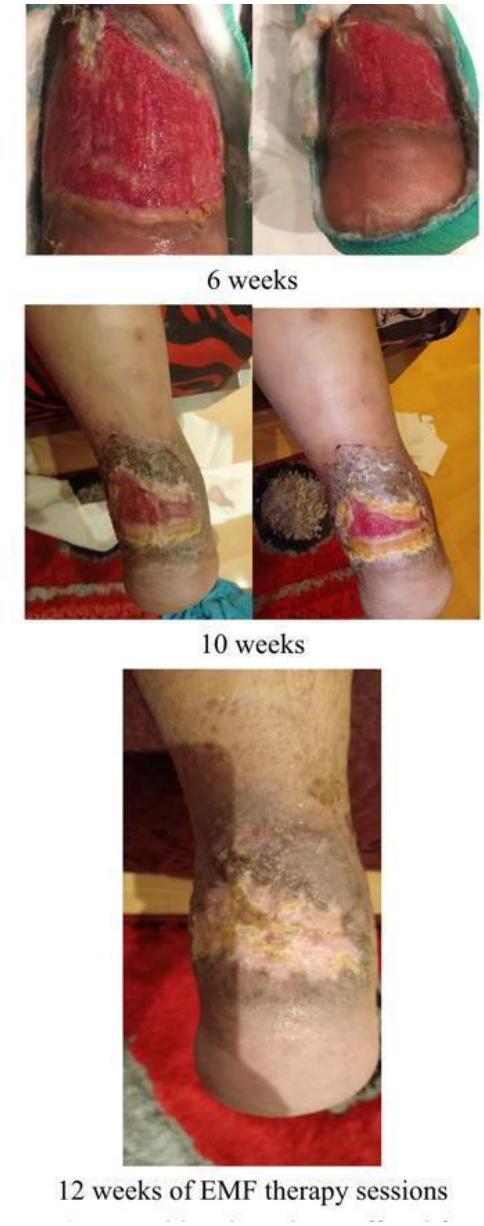

Fig 5: complete wound closure and microbial eradication after 12 weeks

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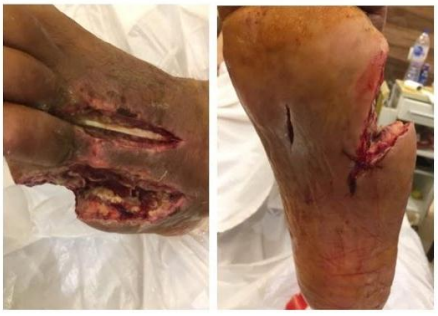

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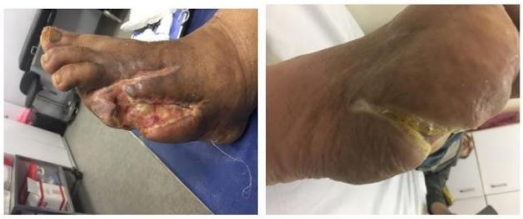
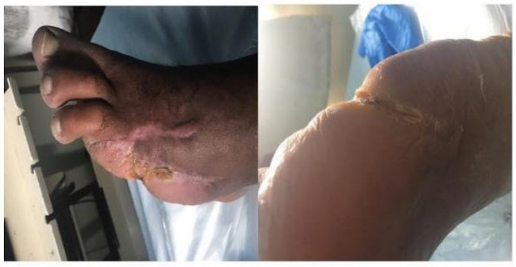


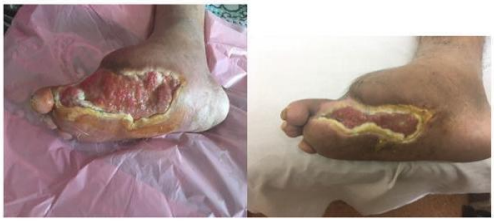
5 weeks of sessions

10 weeks of sessions

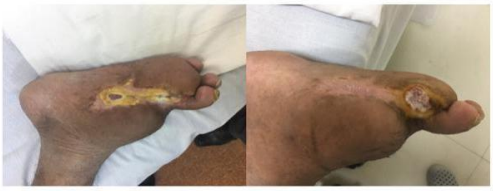


15 weeks of sessions with complete closure

Fig 6: complete wound closure and microbial eradication after 15 weeks

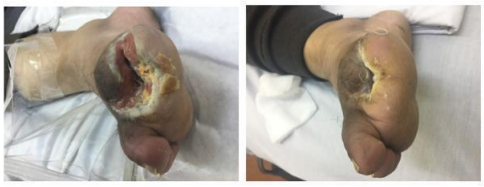


Post debridement 4 weeks



8 weeks 12 weeks

Fig 7: complete wound closure and microbial eradication after 12 weeks



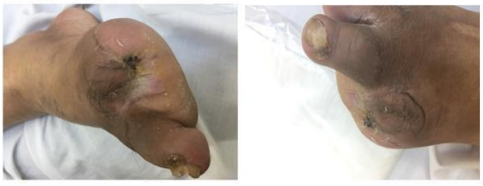
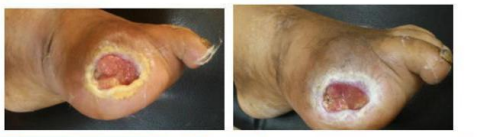


Fig 8: complete wound closure and microbial eradication after 10 weeks



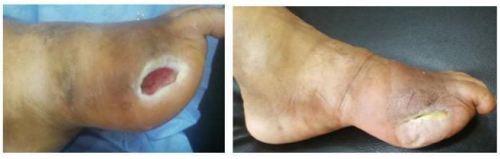


Fig 9: complete wound closure and microbial eradication after 10 weeks

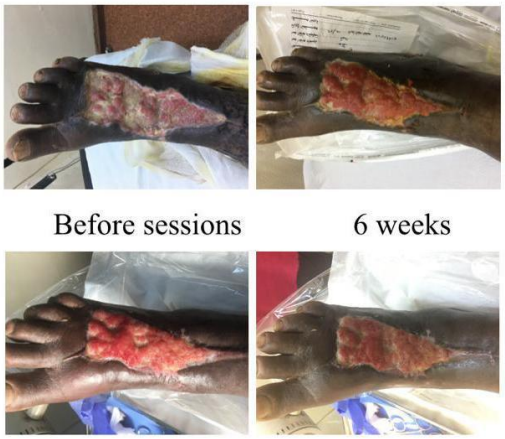


Fig 10: partial closure after 12 weeks

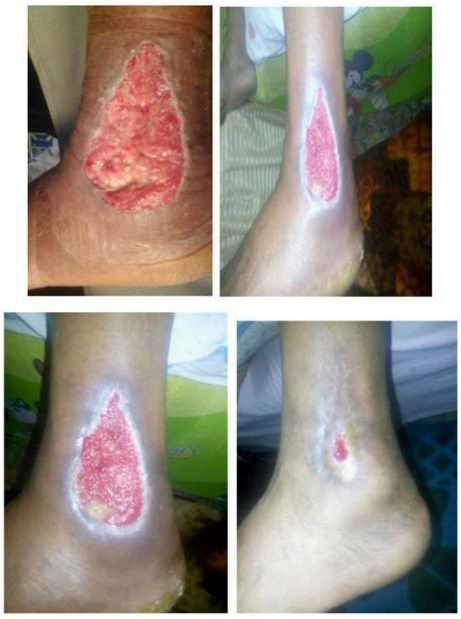


Fig 11: partial closure after 18 weeks

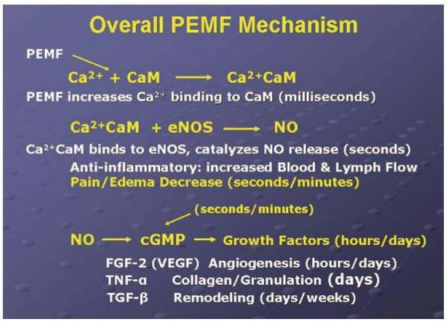


Fig 12: overall PEMF mechanism of wound healing

DISCUSSION

When wound healing does not progress normally, a chronic wound may result and this is a significant burden to both the patient and the medical system. Patients with a single diabetic ulcer or chronic wound carries a high cost in both medical management and follow up, with the number of patients affected growing yearly from 6.5 million, given the increasing prevalence of diabetes and other chronic diseases that may affect wound healing [(9)].

Wound debridement consists of removing necrotic or devitalized tissue and reducing the bacterial load. It is an essential step to bring about wound healing. Numerous debridement methods exist, such as autolytic, enzymatic, biodebridement, and surgical/sharp and mechanical methods. Although sharp debridement using a scalpel or curette remains the gold standard, these techniques have several disadvantages. They are not appropriate for large surfaces, are not optimal for saving tissue, and they often lead to an uneven wound bed **(Bekara et al., 2018).**

Recent innovations, such as hydrosurgery (Versajet), ultrasound therapy (the MIST therapy device), and plasma-mediated bipolar radio-frequency ablation therapy (Coblation) could represent an alternative to conventional debridement in many cases, especially for chronic non-healing wounds [(10)].

Pulsed electromagnetic field (PEMF) has been used clinically as an intervention to enhance healing of chronic ulcers. Previous studies have shown that PEMF accelerated wound closure, reduced wound pain, enhanced healthy granulation and promoted circulation. A systematic review concluded that PEMF could significantly accelerate the healing of chronic ulcers (decubitus, venous and plantar) in patients [(11)]**. (Fig 3, 12).**

Nevertheless, there is a scarcity in the published literature regarding the effect of PEMF on chronic wound healing. Therefore, we performed the present study to evaluate the effect of PEMF therapy on healing of chronic wounds, as regards timing and quality of healing.

In this present prospective non-randomized clinical trial, we included 50 patients with different types of chronic wounds in duration from august 2018 until March 2019. The most

common cause of the chronic wound was diabetes (54%), followed by traumatic ulcer (16%) and decubitus ulcer (10%). While the most commonly causative organism was staph aureus (40%), followed by E. coli (26%) and pseudomonas (20%). **(Table 2).**

In line with our findings, **Sun and colleagues** [(12)] recruited a total of 241 patients from January 1, 2011 to April 30, 2016 with chronic wounds of more than 2 weeks duration from wound healing department in Shanghai, China. Among those patients, the most common cause of chronic wound was diabetes, followed by pressure ulcers.

In addition, **Tzaneva and colleagues** [(13)] performed a cross sectional study on a sample of patients with chronic infected vascular wounds, hospitalized between October 2014 and August 2015, in the Clinic of Vascular Surgery in Trakia Hospital Stara Zagora. The species most frequently isolated were Staphylococcus aureus, E.coli, Enterococcus faecalis, Pseudomonas aeruginosa.

In the present study, 46% of the patients exhibited multidrug-resistant organisms (MDR). The most common MDR species was Staphylococcus aureus (26%) followed by Proteus and strept group a (21.7% for each) then pseudomonas and E.coli (17.3% for each). Multidrug-resistant organisms (MDRO) are increasingly implicated in both acute and chronic wound infections. The limited therapeutic options are further compromised by the fact that wound bacteria often co-exist within a biofilm community which enhances bacterial tolerance to antibiotics [(14)]. In the present study co-existed bacteria within one biofilm were isolated from 9 patients (18%) which considered as a very significant and alarming sign for the increasing prevalence of the mixed infected wounds. **(Table 3).**

Similarly, **Trivedi and colleagues** [(15)] performed a retrospective study comparing the wound infections of 41 diabetic patients to those of 74 non-diabetic patients to test the hypothesis that infections with MDRO were more prevalent in the diabetic population. Overall, the rate of MDRO was almost 50%.

As **Johnson and colleagues** [(16)] advised, treatment begins to treat pain and edema, is generally administered every 4 hours for 30 minutes for 3 days, and then every 8 hours for the next several days until pain and edema are not significant. For the treatment of chronic wounds, the regimen is 30 minutes twice a day until healed, by rate of 3 sessions per week

In terms of the primary outcomes of the present study, 40% of the patients required less than less than 12 sessions of PEMF therapy and 44% of them required 12-24 sessions, while 16% needed more than 24 sessions of therapy by rate of 3 sessions per week to achieve the aimed progress in healing process.

In concordance with our findings, **Gupta and colleagues** [(17)] conducted a randomized trial to assess the effectiveness of PEMF in healing of pressure ulcers in patients with neurological disorders twelve patients with 24 ulcers received PEMF therapy for 30 sessions (45 minutes each). At the end of follow-up, significant healing of ulcers was noted with almost all patients had complete or partial closure of the wound.

Similarly, **Salzberg and colleagues** [(18)] performed a randomized, double-blind study to determine if non-thermal PMEF treatment significantly increased the healing rate of pressure ulcers in patients with spinal cord injuries. Subjects included volunteers admitted to a Veteran's Administration Hospital in New York over a 2 year period and consisted of 30 male spinal cord-injured patients, 20 with Stage II and 10 with Stage III pressure ulcers. The 20 patients with Stage II pressure ulcers, the active group had a significantly increased rate of healing with a greater percentage of the ulcer healed at one week than the control group.

Many pathogenic bacteria synthesize and secrete siderophores; small, high-affinity iron-chelating compounds [(19)]. Siderophore has the ability to bind ferric iron (Fe^{3+}) with an affinity that can exceed that of human Fe^{3+}-binding proteins like transferrin or lactoferrin, enabling siderophores to "steal" iron from these host proteins resulting in iron deficiency anemia [(20)].

Therefore, in the present study we used hemoglobin concentration as a marker for monitoring the prognosis of chronic wounds microbial eradication, which approved obvious relation by 38 improved patients out of 50 (76%) with higher concentration of hemoglobin post microbial eradication.

Similarly, C-reactive protein (C-RP) and white blood cells (WBCs) count were used as markers for monitoring infection and microbial eradication, that's because they both increase

rapidly in concentration following infection. C-reactive protein act as an opsonin enhancing phagocytosis of microbes and activates complement [(21)].

Hence, decreased levels of C-RP concentration and (WBCs) count after exposure to ELF-EM field denotes inhibition of the phagocytosis and opsonization resulting from successful microbial eradication and resolved infection [(22)].

That's why in the present study almost all of the patients revealed a dramatic decrease in C-RP Conc. (98%) and obvious WBCs Count improvement in 45 patients (90%) proving the golden role of EMF therapy in microbial eradication. **(Fig 4).**

To sum up, **Strauch and colleagues** [(8)] performed a systematic review to review the major scientific breakthroughs and current understanding of the mechanism of action of PEMF therapy. A total of 7 studies were included which assessed the efficacy of PEMF in the setting of chronic wound healing. The authors concluded that the rate of wound closure after PEMF therapy ranged between 60-84 %. The included studies also showed decrease in edema and pain after therapy. **(Table 4).**

In the present study, Almost 78% of the patients had complete closure **(Fig 5-9)** and 20% had partial closure **(Fig 10-11)**. Microbial eradication was achieved in 92% of the patients. In addition, pain and edema were improved in 66% of the patients and about 54% of chronic wounds healing was aided by the increased hyperemia**.**

In the present study, we assessed the association between the response to PEMF and clinical characteristics of the patients; the analysis showed that there were statistically significant associations between treatment outcomes and pain ($p = 0.018$), edema ($p = 0.005$), number of sessions ($p < 0.001$), microbial eradication ($p = 0.008$). Such findings are expected as appropriate closure of the wound was reported to be associated with greater reduction in symptoms severity and microbial eradication [(23)].

Although there are no published studies that correlate between the response to PEMF therapy and symptomatic reliefs, previous reports have shown that electrical stimulation therapy improve the severity of symptoms in patients with chronic wounds. **Houghton and colleagues** [(24)] performed a systematic and comprehensive search of four electronic databases to evaluate the effect of electrical stimulation therapy (EST) on wound healing outcomes in adults with various types of chronic wounds. Sixty-two clinical research studies involving 2082 patients with pressure ulcers, venous leg ulcers, diabetic foot wounds, and arterial/ischemic wounds, and ulcers of mixed etiology were located. Results from 22 well-designed randomized clinical trials and 10 high-quality systematic reviews consistently support that EST can improve the symptoms of complete wounds closure compared to patients with partial wound closure.

On the other hand, we found that there were statistically significant associations between complication rates and treatment outcome ($p = 0.008$), microbial eradication ($p < 0.001$), and hospital stay ($p = 0.002$). Such findings can be attributed to the facts that patients with complications are more likely to have poorer outcomes and longer hospital stay [(25)].

Study's Limitations: We acknowledge that the present study has some limitations. This was a cross-sectional study with inherent limitations of possible misclassification and ascertainment bias. In addition, the study was a single-center experience and therefore the results cannot be generalized to the general population.

CONCLUSION

It may be concluded from the present study that the use of EMF therapy waves at specific resonance and frequency proved to be efficient in microbial eradication especially with MDRO, aiding the healing of chronic wounds with several causes and types, besides being noninvasive, safe, fast, least side effects and at low cost.

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