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USE OF PULSED RADIOFREQUENCY ELECTROMAGNETIC FIELD (PRFE) THERAPY FOR PAIN MANAGEMENT AND WOUND HEALING IN TOTAL KNEE AND REVERSE SHOULDER PROSTHESIS: RANDOMIZED AND DOUBLE-BLIND STUDY.

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ABSTRACT

Pulsed radiofrequency Electromagnetic field (PRFE) has a long history about treatment of various medical conditions. Several clinical studies have demonstrated its safety and efficacy as a treatment for pain, edema, and soft tissue injury.
In this pilot, prospective, randomized and double-blind study, a wearable, energy-emitting PRFE therapy device (MetiMed, Performance Hospital Srl, Seriate, Italy) was used to control postoperative pain and to accelerate wound healing in patients who underwent total knee or reverse shoulder prosthesis.
We enrolled in the study 50 consecutive patients who had a total knee arthroplasty or a reverse shoulder prosthesis. The subjects were randomly assigned to receive a placebo or active PRFE device for 20 postoperative days. Postoperative pain was assessed with a 0- to 10-point visual analog scale (VAS). The use of painkillers was also registered. The healing of surgical scars was assessed with Vancouver Scar Scale (VSS) (total score ranging from 0 to 13, with 0 representing normal skin).
Consecutive VAS scores in the 20 days of the study showed no significant decrease in the control group with a day 1 to day 20 difference of 1.48 VAS points. On the other side, VAS score in the study group showed a steady decline (VAS score difference was 4.2 VAS points). The use of painkillers was lower in the group that received PRFE therapy.VSS score in the active group showed a steady decline (day 1 to day 20 difference was 3.92 VSS points) while the VSS scores showed no significant improvement in the placebo group (0.88 VSS points).
According to these findings, PRFE therapy in this form is an excellent, safe, drug-free method of postoperative pain control and wound healing in patients who undergo total knee or reverse shoulder prosthesis.

1. Backgound

Postoperative pain is one of the major priorities for both patients and doctors. Pain affects blood pressure, heart rate, appetite, and general mood. Despite the advances in pain biology research, new analgesics development, and introduction of less invasive surgical procedures, postoperative pain continues to be under-treated (1). Improvement of effective analgesia in the early postoperative period may lead to clinically significant benefits in terms of length of stay, including a decreased incidence of chronic postsurgical pain (2).

Chronic pain after breast cancer surgical treatment, for example, is a major issue affecting 25–60% of patients (3).

Pain control can improve outcomes, shortening hospital stays and convalescences (4, 5).

An underused postoperative pain management method is Pulsed Radiofrequency Energy (PRFE) Therapy, also known as Pulsed Electromagnetic Field Therapy (PEMF), Pulsed Short-Wave Therapy (PSWT), and Radiofrequency (RF) Nonthermal Diathermy.

In 1947, the Federal Communications Commission (FCC) assigned three frequencies at the short end of the RF band (40.68, 13.56, and 27.12 MHz) (6) for medical use.

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The frequency of 27.12 MHz is the most widely used in clinical practice.
Classically, most clinical studies on pain physical therapy analyses PRFE as large and fixed devices, in which therapy is hospital delivered. In our institution, a small, wearable PEMF device (MetiMed, Performance Hospital Srl, Seriate, Italy) was used.
The aim of this prospective, randomized and double-blind study was to evaluate the effects of this PEMF device in patients who underwent total knee or reverse shoulder prosthesis.

2. Material and methods

From September 2015 to April 2016, 50 patients have been included in the protocol; 30 of them underwent total knee arthroplasty implantation and 20 of them reverse shoulder prosthesis.
The study participants provided signed consent forms, and all rights of the enrolled subjects in the present study were protected.
25 active- and 25 placebo-coded devices were mixed in boxes. The patients randomly chose a device, and the device code was recorded.
The device used in this study was a pulsed radiofrequency energy device (MetiMed, Performance Hospital Srl, Seriate, Italy) which emits a safe form of nonionizing electromagnetic radiation. The carrier frequency is 27.12 MHz, the assigned Federal Communications Commission medical frequency, and it has a pulse rate of 1000 pulses/s. The circuitry consists of low voltage (1 Vpp) digital/analog electronics that controls all timing functions to produce the therapeutic radiofrequency field, with the antenna field placed directly above the therapeutic site. The described system transfers radiofrequency energy to tissues to obtain the desired biological effect. The placebo devices didn't emit anything, but were identical to the active devices. The active devices couldn't be distinguished in any way from the placebo devices.
Once the surgery was completed, the PRFE devices were activated and secured in place on the knee or shoulder surgical wound with a wrap and removed 20 days after surgery.
Pain was assessed using a visual analog scale (VAS) ranging from 0 (no pain) to 10 (extreme pain. The use of analgesics (paracetamol or NSAID's) was also recorded.
The surgical wound was evaluated using a score system. The Vancouver Scar Scale (VSS), as reported in Table 1, is the most widely used outcome scale for scars (8). The results range from 0 to 13, with 0 representing normal skin. VSS has also been validated to rate postsurgical scars (9).
Photographs of the scars have been taken 24 hours postoperatively, then on days 3, 7 and 20 when sutures were removed.
Mean and standard deviations are reported. The differences between active and placebo groups were determined by t-tests and Friedman tests for nonparametric repeated measures. A p-value < 0.05 was considered significant.

3. Results

No patients were lost to follow-up. Data were obtained from all the 50 enrolled patients and were available for statistical analysis. The demographic data indicated that the randomization was successful.

Vascularity	normal	**0**
	pink	**1**
	red	**2**
	purple	**3**
Pigmentation	normal	**0**
	hypopigmentation	**1**
	mixed	**2**
	hyperpigmentation	**3**
Pliablity	normal	**0**
	firm	**1**
	ropes	**2**
	contracture	**3**
Height	flat	**0**
	<2 mm	**1**
	>2 mm <5 mm	**2**
	>5 mm	**3**

Table 1 - Vancouver Scar Scale (VSS): 0=best; 12=worst.

No significant difference was found among age (70.4 vs 71.5), height (1.66 cm vs 1.63 cm), weight (78 vs 76), sex (18 women/7 men vs 20 women/5 men) or type of surgery (20 knees/5 shoulders vs 18 knees/7 shoulders) between the 2 groups (active vs placebo).
The PRFE therapy devices were well tolerated by all the patients, and no adverse effects were reported. Mean VAS scores with SD are showed in Table 2.

	VAS Score, mean ± SD	
day	Control Group (n=25 patients)	Study Group (n=25 patients)
1	6.36±2.75	6.2±2.77
2	6.04±2.49	6.16±2.47
3	5.72±1.99	4.84±2.34
4	5.6±2.23	5±2.55
5	5.6±1.89	5.08±2.21
6	5.28±2.07	5.08±2.31
7	4.72±1.94	4.4±2.18
8	4.76±1.81	4.6±2.22
9	4.72±1.72	4.52±2.27
10	4.8±1.75	4.44±2.16
11	5±1.98	4.08±2.16
12	5.28±2.13	3.96±2.28
13	5.44±2.2	3.56±1.91
14	5.28±2.30	3.48±2.18
15	5.2±2.14	3.2±2.16
16	5.12±2.09	2.88±1.81
17	5±1.98	2.52±1.68
18	4.96±2.15	2.48±1.85
19	5.04±2.26	2.32±1.72
20	4.88±2.18	2±1.55

Table 2 - Mean visual analog scale scores (N= 50 patients). Data presented as mean ± standard deviations. Friedman test for nonparametric repeated measures showed significant difference (p=0.033) between mean values for control and study groups.

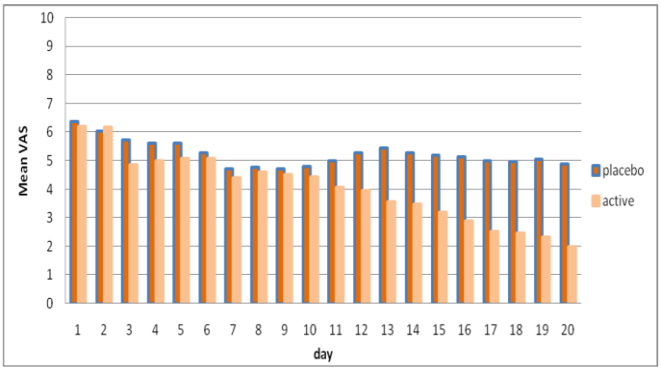

Figure 1 - The mean pain level in the study group were significantly lower compared to the control group using the placebo device

The F test was performed using Excel 2007 QI macros and it showed a significant difference (p=0.033) between mean values for control and study groups.

On day 1 post-operative VAS scores were not significantly different between study and control groups. On day 20 of post-operation, VAS pain scores showed an improvement in pain control as a mean difference in VAS score of 1.48. In contrast, the VAS score in the study group showed a steady decline (Figure 1). From day 1 to day 20, VAS score mean difference was 4.2 points.

The VAS scores from day 2 through day 20 were compared with the day 1 VAS scores using the Student's t test (Table 3).

	p value	
day	Control Group (n=25 patients)	Study Group (n=25 patients)
2	0.6683	0.9572
3	0.3507	0.0667
4	0.2892	0.1174
5	0.2609	0.1208
6	0.1235	0.1268
7	0.0187*	0.0138*
8	0.0189*	0.0287*
9	0.0148*	0.0232*
10	0.0208*	0.0156*
11	0.0505	0.004*
12	0.1273	0.003*
13	0.1979	0.0002*
14	0.1387	0.0003*
15	0.1027	<0.0002*
16	0.0789	<0.0002*
17	0.0505	<0.0002*
18	0.0506	<0.0002*
19	0.0701	<0.0002*
20	0.0404*	<0.0002*

Table 3 - VAS scores on day 2 through day 20 compared with day 1 score using Student's t test. (N= 50 patients) - (* Statistically significant difference.)

The VAS scores from day 2 to day 20 in the control group show no significant differences compared with the day 1 scores. In contrast, the steady decline in pain scores in the study group have become significantly different at day 4 (p=0.01) compared with the day 1 score. The decline in pain continued to be significant until day 20.

Patients in both groups could take paracetamol or NSAID's as painkillers medicaments. Patients from the placebo group took 157 pills in total, while patients from the study group took 84 pills. Not one patient from the active group used more than 10 painkillers. Five patients in the placebo group used 10 or more pills.

Statistical analysis of analgesic consumption is shown in Table 4. Pill intake means were 3.36 pills per patient in the active group and 6.28 pills per patient in the placebo group. The mean VSS scores on days 1-3-7-20 are shown in Table 5.

	Total	Mean	SD	Median
Control Group (n=25 patients)	157	6.28	3.33	6
Study Group (n=25 patients)	84	3.36	1.77	3

Table 4 - Total pills used by patient group.

	VAS Score, mean ± SD	
day	Control Group (n=25 patients)	Study Group (n=25 patients)
1	7.16±1.97	6.2±2.31
3	7±2.24	5.24±2.06
7	6.68±2.61	3.88±1.71
20	6.28±2.73	2.28±1.86

Table 5 - Mean Vancouver Scar Scale (N= 50 patients) for the 1-3-7-20 days of the study. Data presented as mean ± standard deviations.

The VSS score in the active group showed a steady decline (difference from day 1 to day 20 was 3.92 VSS points, p< 0,01); while in the placebo group there was no significant decline (day 1 to day 20 difference was 0.88 VSS points, p= 0,2) (Figure 2). VSS scores on day 3-7-20 were compared with the day 1 VSS scores using the Student's t test (Table 6). The steady decline in scar scores in the study group had become significantly different at day 7 (p<0.01) compared with the day 1 score, while in the control group there were no significant differences.

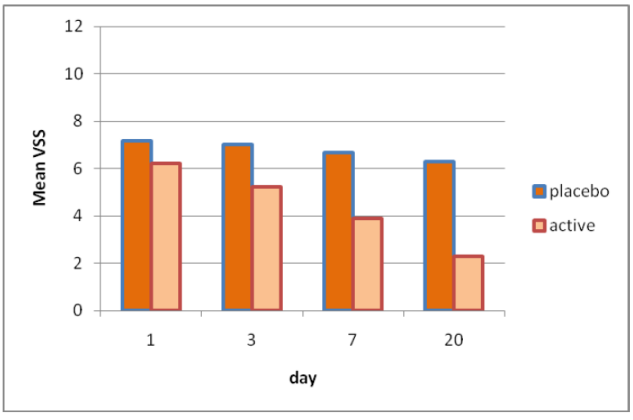

Figure 2 - The mean VSS of the study group compared to the control group using the placebo device (1-3-7-20 days of the study).

	p value	
day	Control Group (n=25 patients)	Study Group (n=25 patients)
3	0.7896	0.128033251
7	0.4666	<0.0002*
20	0.1977	<0.0002*

Table 6 - VSS scores on day 3-7-20 compared with day 1 score using Student's t test. (N= 50 patients) - (* Statistically significant difference.)

4. Discussion

The first PRFE device, the Diapulse (Diapulse Corporation, Great Neck, NY, USA), was made commercially available in the 1950s. It was followed by other commercially machines made available. As a treatment for nonhealing bone fractures in humans, the use of PEMF is well established (10) and has been in use since the 1970s. Clinical studies demonstrated its safety and efficacy as a treatment for pain, edema, and soft tissue injury. Some of the first studies investigating postoperative edema and edema caused by soft tissue injury showed promising results (11,12). Studies on postoperative pain also showed good results (13-15). Reduction of capsular contraction in 41 patients after breast augmentation surgery was achieved with PRFE therapy together with massage and closed capsulotomy treatment (16). Pain and edema have also been treated with PRFE therapy in different orthopedic conditions (6, 17–20). Other findings also demonstrated that PRFE therapy can be effective for chronic wounds, including diabetic and venous stasis ulcers. A number of early studies showed good results (21), with improved healing of pressure ulcers with PRFE treatment (22).

A prospective, randomized, double-blind, placebo-controlled multicenter study assessed the clinical efficacy and safety of pulsed electromagnetic therapy delivered by a portable device. The device was used at home to heal recalcitrant wounds, predominantly venous leg ulcers; significant decreases in wound depth and pain intensity were observed (23).

Some recent studies about use of PRFE for the treatment of chronic wounds may bring a new focus to its application in this field (22–25), including a retrospective study on the Regenesis Biomedical Wound-Healing Registry (26) (Regenesis Biomedical, Scottsdale, AZ, USA).

Two studies on postoperative pain using a wearable form of PRFE from Ivivi Technologies (SofPulseTM; Ivivi Technologies, Northvale, NJ, USA) have been reported. In the first study, a double-blind, placebo-controlled, randomized clinical trial on breast augmentation showed a significant decrease in postoperative pain (28). The second study, using the same form of wearable PRFE device after breast reduction surgery, also showed significant control of postoperative pain (29). In this study, a decrease in interleukin 1-b was reported, suggesting that the biological action of these devices can induce modulation of the wound-healing process.

A potential mechanism of action for PRFE therapy has been put forward and reviewed by Strauch et al. (30). Moreover, recent reports have further contributed to understanding the mechanisms of PRFE therapy for wound healing (31, 32).

While the exact mechanism by which PEMF interacts with cells to initiate the therapeutic effects is not fully understood, cell studies have given valuable insight into the downstream biological effects of PEMF therapy. Human fibroblasts exposed to PEMF signal showed p42/44 MAP kinase activation (33), and an increased cell proliferation. The MAP kinase family of intracellular signaling proteins is activated by a range of stimuli and the activated MAP kinase translocate into the nucleus and transactivate transcription factors, changing gene expression to promote growth, differentiation or proliferation. Co-cultures of human epidermal keratinocytes and human dermal fibroblasts, studied by gene array, demonstrated an up-regulation of gene families associated with every phase of the wound healing cycle (34, 35). These included many genes involved in the inflammatory stage of wound repair and expression of genes involved in angiogenesis and tissue remodeling.

Cell studies on human vascular endothelial cells confirm angiogenesis effects of PEMF fields (36), as well as upregulation of FGF-2 (37), a growth factor that promotes angiogenesis. Nitric oxide is upregulated by PEMF, nitric oxide is a vasodilator and also promotes angiogenesis (38).

In mouse models of diabetes, wound healing rates were increased when exposed to

PEMF, compared to animals that were sham PEMF treated (39). A notably increased proliferation of dermal fibroblasts was determined, measured by the cell proliferation marker Ki67, a protein that accumulates in the cell nucleus of cells progressing through the cell cycle.

Our study showed that patients who received PRFE therapy experienced significantly less postoperative pain than the patients assigned the placebo devices.

Because VAS scores are a measure of the pain level, it is interesting to note that the sum of the mean VAS points for each day resulted in an accumulated average total of 104.8 VAS points for the placebo patient group and 80.8 VAS points for the active group during the 20-day study period. This indicates that the active group patients experienced an average of 23% less pain than those who received the placebo device. This is a considerable decrease in postoperative pain.

It also must be considered that the placebo patients were still experiencing 76.7% of the baseline VAS score, whereas the active group had 32.2% of the baseline VAS score remaining. Thus, the placebo group continued to experience significant pain beyond day 20.

Data also showed that patients who received PRFE therapy required less pain medication (an average of 46.5%).

Taken together, decreased postoperative pain and lower medication use suggest that postsurgical complications would be reduced and that pain medication-related side effects would also be less frequent.

These data therefore indicate that PRFE is a safe and effective method for combating postoperative pain.

Furthermore, the patients who received PRFE therapy had a better wound healing. (Figure 3a-4b/4a-4b). In fact, the VSS score in the active group showed a steady decline while the VSS scores showed a consistency in the control group.

The PRFE device used in the present study is based on work pioneered by Bentall (40) in the 1980s; he first showed that reducing the power and size but extending the use time produced equivalent results to larger and more powerful devices.

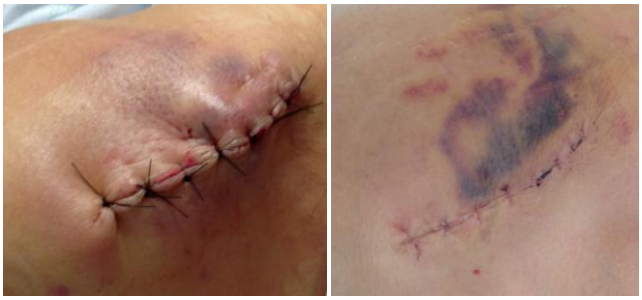

Figure 3 a/b - Patient who underwent reverse shoulder prosthesis with placebo device at the day 1 and after 20 days

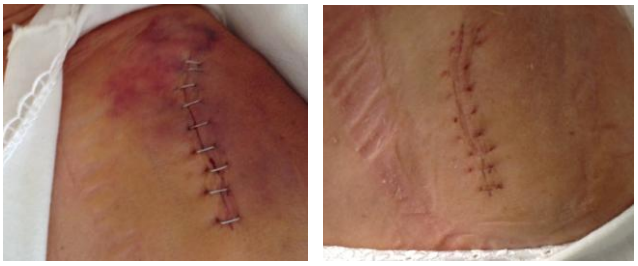

Figure 4 a/b - Patient who underwent reverse shoulder prosthesis at the beginning of PRFE treatment (day 1) and after 20 days PRFE therapy.

A study by Nicolle and Bentall (41) on surgical recovery showed that the extended-use of PRFE devices were able to control edema after blephoraplasty.

There has been a new focus on small, extended-use PRFE devices, and a number of studies on postoperative recovery and wound healing have been published (42–45).

PRFE therapy for postoperative pain and wound healing appears to offer a therapy that is easy to use, noninvasive, and drug free, with no reported side effects.

5. Conclusions

The results from the present initial study show that PRFE therapy can produce a relatively rapid pain control. However, the present study had a number of limitations, including lack of long-term follow-up, and the single center study design that may have altered blindness.

Larger-scale clinical trials are still needed for further validation of this postoperative therapy. However, previous findings and our results have shown that the use of PRFE therapy in a clinical setting is effective.

Given the clear need to improve postoperative analgesia and wound healing, extended-use low-energy PRFE devices potentially offer a new dimension to multimodal analgesic techniques, considering that the PRFE therapy has a long history of use and that side effects have not been reported. This postoperative pain management, associated with improved wound healing, could be used in almost every situation, allowing for a greater flexibility in the use of pharmacologic therapy.

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