



Physics & Clinical Evidence of Pulsed Shortwave Frequency Therapy

*For the Reduction of Pain, Inflammation
and Accelerated Healing*

BioElectronics Corporation

4539 Metropolitan Court, Frederick, Maryland 21704 USA

P: +1-301-874-4890 | F: +1-301-874-6935

E: info@bielcorp.com | W: www.bielcorp.com

Wall Street Journal Technology Award



BioElectronics Corporation pulsed radio frequency electromagnetic field therapy, is changing the way people heal. BioElectronics has taken an old established technology delivered by large expensive machines and made it accessible for all. By reducing the size, to a lightweight wearable device, and extending the time of the therapy, patients can go about their daily lives receiving therapy every minute of the day. Clinical studies, some published in the 1960's showed that the energy of RF electromagnetic field had great therapeutic value. Patients had significantly improved pain, faster healing times and improved function. Challenging chronic wounds were also shown to be effectively treated. The major obstacle to the wide use of this therapy has not been the clinical effectiveness, or the safety. In fact, in all the published clinical studies there were no reports of detrimental side effects, in fact no side effects at all. The size of the devices and cost has been the reason that this therapy is not widely employed in clinical practice. For example, healing of wounds requires two 30 minute treatments per day, effectively limiting its use to the most severe cases. Now all that has changed, with peer reviewed clinical studies published in established medical journals, it's now becoming clearer than ever that BioElectronics devices have the same therapeutic efficacy of reducing pain and promoting healing as the established large clinical devices. The significance difference is that Bioelectronics devices are economical, simple to use, easy to wear and portable.

Table of Contents

WOUND HEALING	005
MEDICAL APPLICATIONS - SHORTWAVE RADIO FREQUENCY	006
A THERMAL COMPONENT OF PULSED RADIO FREQUENCY ENERGY THERAPY.....	007
NON-THERMAL MECHANISM OF ACTION OF PULSED RADIO FREQUENCY	
ELECTROMAGNETIC FIELDS	008
ELECTRIC FIELDS AND THE ENHANCEMENT OF WOUND HEALING.....	012
PULSED RADIO FREQUENCY DEVICE INNOVATION	013
EXTENDED TREATMENT TIME PULSED RADIO FREQUENCY STUDIES...	014
R. H .C. BENTALL LOW-LEVEL PULSED RADIOFREQUENCY FIELDS AND THE	
TREATMENT OF SOFT-TISSUE INJURIES	015
Confirming Animal Studies	033
Extended time low power clinical studies	033
ACTIPATCH USER SURVEY.....	038
Survey Results	039
Results Back Pain.....	043
ActiPatch compared to therapies for Back Pain.....	045
ActiPatch v NSAID's/Paracetamol for Back Pain.....	045
Results Knee Pain.....	048
BIOELECTRONICS CLINICAL STUDIES	051
CONTROL OF POST-OPERATIVE REACTION I IN BLEPHAROPLASTY.....	051
CONTROL OF POST-OPERATIVE PAIN	054
The use of a portable, wearable form of pulsed radio frequency electromagnetic energy	
Device for the healing of recalcitrant ulcers	060
PULSED RADIOFREQUENCY ELECTROMAGNETIC FIELD THERAPY IS AN EFFECTIVE	
WOUND PAIN THERAPY.....	066
PULSED RADIOFREQUENCY ELECTROMAGNETIC FIELD: A POTENTIAL NOVEL	

THERAPY FOR DIABETIC PERIPHERAL NEUROPATHY PAIN	068
ADJUNCT WOUND HEALING THERAPY	070
Pyoderma Gangrenosum cutaneous skin ulcers with chronic pain.....	075
Plantar Fasciitis.....	088
Differentiation of Osteoprogenitor cells into bone	093
Pulsed Radio Frequency Electromagnetic Field Therapy: A Potential Novel Treatment for Pain and Inflammation of Delayed Onset Muscle Soreness	101
Menstrual Pain.....	107
PHYSICIAN CONDUCTED PILOTS AND TESTIMONIALS.	117
ActiPatch and Rapid Recovery	117
ACTIPATCH - A New way of treatment, Pilot investigation of 52 patients in general praxis	118
ActiPatch Therapy Following Cosmetic Surgery of the Face and Neck: A Valuable Adjunct to The Postoperative Management	120
Abdominoplasty Post-Operative Pain Control with ActiPatch	123
MARKET CLEARANCES	127
TESTIMONIALS.....	128

BioElectronics Corporation

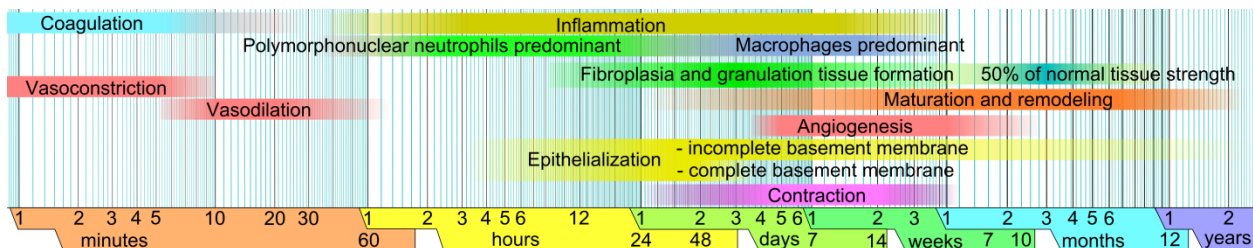
Pulse Radio Frequency Electromagnetic Energy

Energy for Healing

Wound healing is a complex process that involves inflammation, cell proliferation, formation of granulation tissue, production of new structures and tissue remodeling. Healing of all tissue injury involves these phases of healing, and normally results in scar tissue formation.

Pulsed radio frequency electromagnetic energy, through decades of research has been shown to significantly shorten each phase of the wound healing process. By reducing the inflammation phase, increasing cell proliferation and activity leading to the combined and coordinated effects of wound contracture and granulation tissue maturation associated with collagen deposition, with the end result reflected in an accelerated healing response.

PHASES OF HEALING



Introduction

MEDICAL APPLICATIONS - SHORTWAVE RADIO FREQUENCY

Therapeutic medical application of radio frequency (RF) energy at a carrier frequency between 13–27.12MHz is referred to as shortwave diathermy and can be divided into two general categories based on mode of delivery: continuous RF energy delivery and pulsed RF energy delivery. Continuous delivery of shortwave energy to a tissue leads to an increase in tissue temperature, and is used for the therapeutic delivery of deep heat. Delivery of pulsed RF energy to a tissue can allow for the dissipation of heat between pulses, providing therapeutic effects in the absence of substantial tissue temperature elevation, a therapy first developed to diminish negative complications that can occur with tissue heating, while conserving other therapeutic benefits of this type of application. While tissue heating with pulsed RF energy is deemed to be insignificant, new research suggests that there is a thermal component to pulsed RF energy which may offer significant therapeutic effects on soft tissues. Pulsed RF energy has a wide range of therapeutic uses, is well tolerated due to the non-invasive nature of application, and serves as an effective adjunctive treatment for many conditions. Non thermal therapeutic uses of pulsed radio frequency are currently being used to treat pain and edema, chronic wounds, and bone repair.

Pulsed radio frequency electromagnetic field therapy (PRFE), or pulsed electromagnetic field (PEMF) therapy has a long history in treating medical conditions. In 1947 the Federal Communications Commission assigned three frequencies at the short end of the RF band for medical use (40.68 MHz, 13.56 MHz and 27.12 MHz). The frequency of 27.12 MHz is the most widely used in clinical practice. The first PRFE device, the Diapulse (Diapulse Corporation, NY) was commercially available in the 1950's, and was followed by other commercially available machines. PRFE is a non-invasive therapy that delivers electromagnetic energy into soft tissue generating an electric field which is thought to mediate the therapeutic effects. BioElectronics Corporation range of pulsed radio frequency electromagnetic energy devices operate in the shortwave form of 27.12Mhz.

A Thermal Component of Pulsed Radio Frequency Energy Therapy?

We gratefully acknowledge that the following section is the work of Professor Tim Watson (Professor Tim Watson, School of Health & Emergency Professions, University of Hertfordshire, UK) and can found at www.electrotherapy.org.

The peripheral neural system is now known to be highly temperature sensitive, and many other specific sites and mechanisms of thermal sensitivity have been identified. Temperature increases in tissues as low as 0.1°C have significant biological affects which include:

- Vasodilation
- ↑rate of cell metabolism
- ↑ capillary permeability
- ↑delivery of leukocytes

- Removal of metabolic waste
- ↑ elasticity of ligaments, capsules, and muscle
- Analgesia and sedation of nerves
- ↑ nerve conduction
- ↓ muscle tone
- ↓ muscle spasm

The early development of RF energy application was termed diathermy, which literally means heating through. Termed, because unlike externally applied heat the RF energy is able to penetrate relatively deep into soft tissue resulting in a deep heating effect. Pulsing was introduced to eliminate these heating effects and reduce the adverse effects of heat induced tissue damage. However, pulsing the RF energy has proven to eliminate thermal damage a thermal therapeutic effect cannot be ruled out. Recent research suggests that a thermal component of pulsed RF energy may still be a factor in the therapeutic effects of PRFE. With respect to the effects of pulsed shortwave diathermy, there is an element of tissue heating which occurs during the 'on' pulse, but this is dissipated during the prolonged 'off' phase. Clearly during the delivery of each pulse there will be a (very small) thermal change and the potential thermal effect of pulsed short wave is dependent on 3 parameters:

Pulse Repetition Rate (Hz or pps)

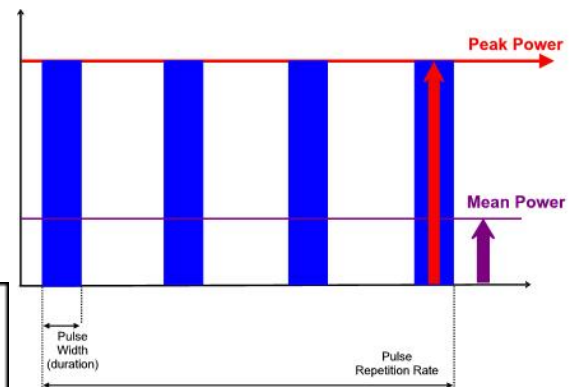
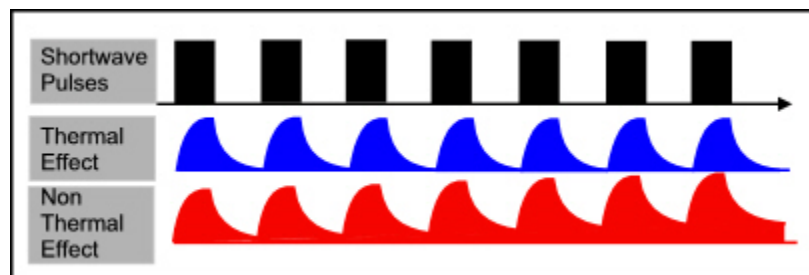
the number of pulses delivered per second

Pulse Duration (Width) (microseconds)

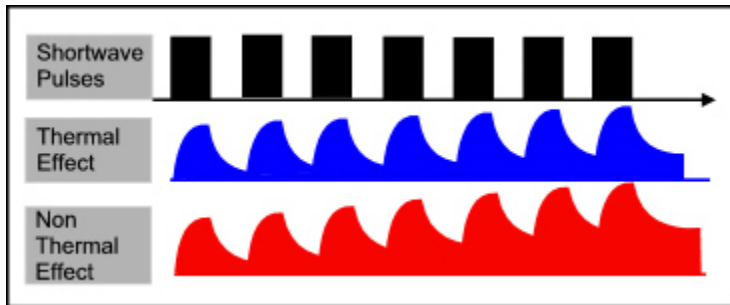
the duration (time) of each 'ON' phase

Power (Peak and Mean)

power delivered from the device (during pulse - PEAK and averaged over time to - MEAN)



In this example the pulse rate is sufficiently spaced so that there is no thermal build up.



In this example a high pulse rate results in a non-thermal and thermal build up.

The externally applied continuous application of low level heat has recently shown to be therapeutically effective in a series of clinical studies. However, externally applied low level heat results in minimal deep tissue heating. Pulsed RF as a continuous application is able to apply physiologically significant levels of heat deep into the target tissue, without and corresponding negative effects of thermally induced tissue damage. The dual thermal and electrical therapy of pulsed RF electromagnetic energy provides a unique dynamic approach to pain reduction and the acceleration of healing.

Non-Thermal Mechanism of Action of Pulsed Radio Frequency Electromagnetic fields

The mechanism of action of Pulsed Radio Frequency Electromagnetic Field (PRFE) on wound healing and control of pain is beginning to be understood based on a number of cell and animal studies. The mechanism of Ca^{2+} calmodulin signaling leading to nitric oxide (NO) production is covered by a review article Strauch et al 2009 and a figure from the article is presented below (Strauch, Herman et al. 2009).

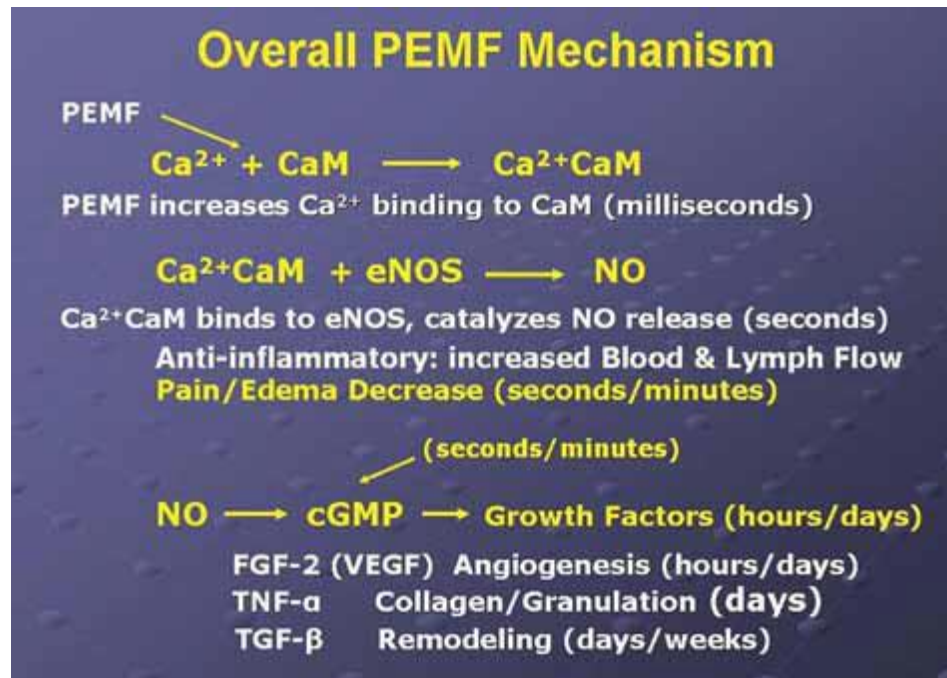
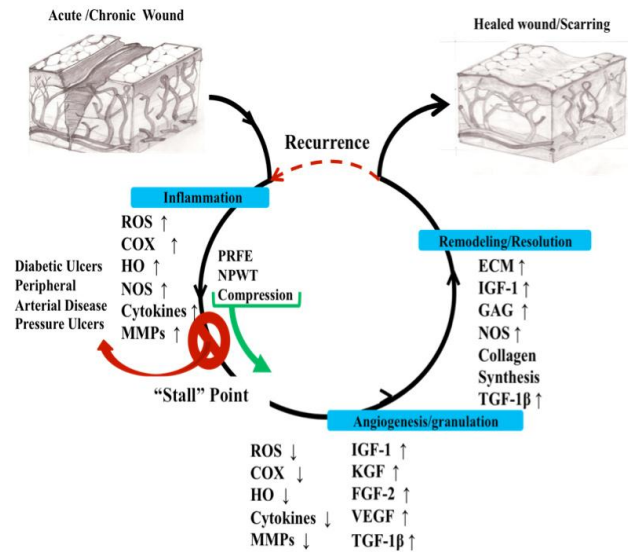


Figure 1. A proposed model for Pulsed electromagnetic field (PEMF) transduction mechanism based on evidence to date that many athermal PEMF effects depend upon nitric oxide cascades. PEMFs can be configured to modulate calcium-binding kinetics to calmodulin. Calcium/calmodulin then activates nitric oxide synthase and the relevant cascade ensues dependent upon stage of tissue repair process. This mechanism has been proposed as a working model for PEMF therapeutics.

A number of cellular studies show PRFE has effects on production of nitric oxide(Diniz, Soejima et al. 2002; Kim, Shin et al. 2002; Fitzsimmons, Gordon et al. 2008; Yue, Yang et al. 2008; Lee, Kwon et al. 2010), increased cell proliferation(Diniz, Soejima et al. 2002; Kim, Shin et al. 2002; Fitzsimmons, Gordon et al. 2008; Yue, Yang et al. 2008; Lee, Kwon et al. 2010), and in vivo vasodilation in rat muscle(Smith, Wong-Gibbons et al. 2004). It is known that NO is a critical molecular signal and mediator for normal wound healing(Boykin 2010; Filippin, Cuevas et al. 2011), and NO deficiency has been established as an important mechanism responsible for poor healing in diabetic foot ulcer patients(Filippin, Cuevas et al. 2011).

Co-cultures of human dermal fibroblasts and human epidermal keratinocytes exposed to PRFE demonstrated an up-regulation of gene families involved in tissue repair. These include matrix metalloproteinase (MMP,s) and tissue inhibitor of metalloproteinase (TIMP's), and cytokines - interleukin (IL)-related genes, interferon (INF)-related genes, and tumor necrosis factor (TNF)-related genes (attached).



The growth factor, fibroblast growth factor-2 (FGF-2) has also been shown to be up-regulated by PRFE treatment. FGF-2 promotes endothelial cell proliferation and the physical organization of endothelial cells into tube-like structures, thus promoting angiogenesis. As well as stimulating blood vessel growth, FGF-2 is an important player in wound healing, stimulating proliferation of fibroblasts and endothelial cells that give rise to angiogenesis, and developing granulation tissue as well as increasing blood supply. A number of animal and cell studies have demonstrated FGF-2 up-regulation after PRFE treatment. In a mouse model of diabetes, PRFE treatment improved healing with the up-regulation of FGF-2 and was able to prevent tissue necrosis in diabetic tissue after an ischemic insult (Callaghan, Chang et al. 2008). Angiogenesis mediated by FGF-2 up-regulation as well as angiopoietin-2 was reported in bones of mice treated with PRFE (Goto, Fujioka et al. 2010). A study on endothelial cells treated with PRFE also demonstrated a FGF-2 up-regulation and increased endothelial tubular formation with the effects mitigated by FGF-2 neutralizing antibody (Tepper, Callaghan et al. 2004). Though not significant, FGF-2 was shown to be up-regulated in wounds after breast reduction surgery (Rohde, Chiang et al. 2010). Taken together these studies indicate that PRFE therapy can up-regulate mechanisms involved in tissue repair including growth factors and cytokines important for the wound healing process.

The medical applications of PRFE therapy have recently been well reviewed by Guo et al (Guo, Kubat et al. 2011).

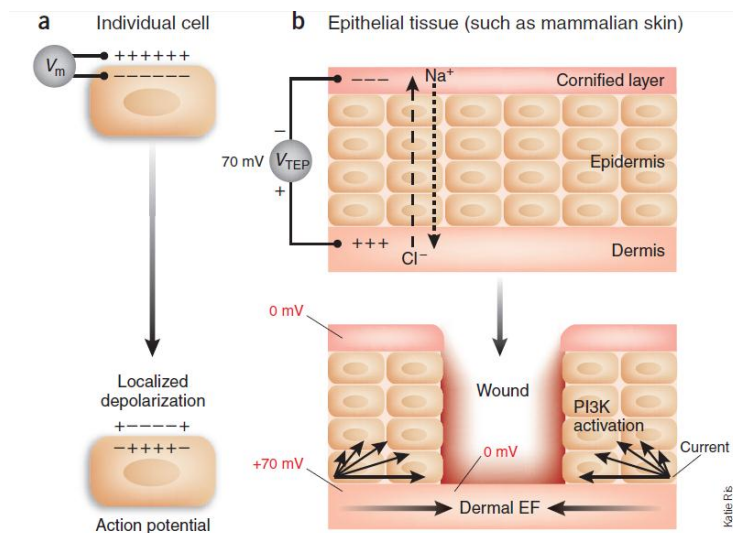
References

- Boykin, J. V., Jr. (2010). "Wound nitric oxide bioactivity: a promising diagnostic indicator for diabetic foot ulcer management." *J Wound Ostomy Continence Nurs* 37(1): 25-32; quiz 33-24.

- Callaghan, M. J., E. I. Chang, et al. (2008). "Pulsed electromagnetic fields accelerate normal and diabetic wound healing by increasing endogenous FGF-2 release." Plast Reconstr Surg **121**(1): 130-141.
- Diniz, P., K. Soejima, et al. (2002). "Nitric oxide mediates the effects of pulsed electromagnetic field stimulation on the osteoblast proliferation and differentiation." Nitric Oxide **7**(1): 18-23.
- Filippin, L. I., M. J. Cuevas, et al. (2011). "Nitric oxide regulates the repair of injured skeletal muscle." Nitric Oxide **24**(1): 43-49.
- Fitzsimmons, R. J., S. L. Gordon, et al. (2008). "A pulsing electric field (PEF) increases human chondrocyte proliferation through a transduction pathway involving nitric oxide signaling." J Orthop Res **26**(6): 854-859.
- Goto, T., M. Fujioka, et al. (2010). "Noninvasive up-regulation of angiopoietin-2 and fibroblast growth factor-2 in bone marrow by pulsed electromagnetic field therapy." J Orthop Sci **15**(5): 661-665.
- Guo, L., N. J. Kubat, et al. (2011). "Pulsed radio frequency energy (PRFE) use in human medical applications." Electromagnetic biology and medicine **30**(1): 21-45.
- Kim, S. S., H. J. Shin, et al. (2002). "Enhanced expression of neuronal nitric oxide synthase and phospholipase C-gamma1 in regenerating murine neuronal cells by pulsed electromagnetic field." Exp Mol Med **34**(1): 53-59.
- Lee, H. M., U. H. Kwon, et al. (2010). "Pulsed electromagnetic field stimulates cellular proliferation in human intervertebral disc cells." Yonsei Med J **51**(6): 954-959.
- Nicolle, F. V. and R. M. Bentall (1982). "Use of radio-frequency pulsed energy in the control of postoperative reaction in blepharoplasty." Aesthetic Plast Surg **6**(3): 169-171.
- Rawe, I. M. and T. C. Vlahovic (2011). "The use of a portable, wearable form of pulsed radio frequency electromagnetic energy device for the healing of recalcitrant ulcers: A case report." Int Wound J.
- Rohde, C., A. Chiang, et al. (2010). "Effects of pulsed electromagnetic fields on interleukin-1 beta and postoperative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients." Plast Reconstr Surg **125**(6): 1620-1629.
- Smith, T. L., D. Wong-Gibbons, et al. (2004). "Microcirculatory effects of pulsed electromagnetic fields." J Orthop Res **22**(1): 80-84.
- Strauch, B., C. Herman, et al. (2009). "Evidence-based use of pulsed electromagnetic field therapy in clinical plastic surgery." Aesthet Surg J **29**(2): 135-143.
- Tepper, O. M., M. J. Callaghan, et al. (2004). "Electromagnetic fields increase in vitro and in vivo angiogenesis through endothelial release of FGF-2." FASEB J **18**(11): 1231-1233.
- Yue, A., G. Yang, et al. (2008). "[The influence of the pulsed electrical stimulation on the morphology and the functions of the endothelial cells]." Sheng Wu Yi Xue Gong Cheng Xue Za Zhi **25**(3): 694-698.

Electric Fields and the Enhancement of wound healing

Pulsed radio frequency electromagnetic fields result in two basic fields: the electric field and magnetic fields that are generated in the soft tissue. It is these fields and the currents generated in the soft tissue that are thought to cause the heat for the thermal component and the currents that can exert changes in cellular activity. It has been known for many years that endogenous DC electric fields are important, fundamental components of development, regeneration, and wound healing. The fields are the result of polarized ion transport and current flow through electrically conductive pathways. Blocking of endogenous electric fields with pharmacological agents or applied electric fields of opposite polarity disturbs the aforementioned processes, while enhancement increases the rate of wound closure and the extent of regeneration. Electric fields are applied to humans in the clinic, to provide an overwhelming signal for the enhancement of healing of chronic wounds. Although clinical trials, spanning a course of decades, have shown that applied electric fields enhance healing of chronic wounds, the mechanisms by which cells sense and respond to these weak cues remains unknown. Electric fields are thought to influence many different processes *in vivo*. However, under more rigorously controlled conditions *in vitro*, applied electric fields induce cellular polarity and direct migration and outgrowth.



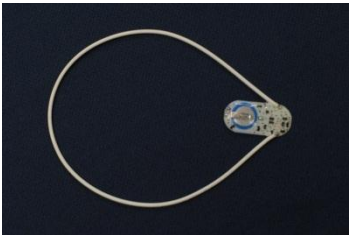
Action potential in individual cells and injury potential in tissues. **(a)** Individual cells maintain an electrical potential across the plasma membrane (V_m) as a result of the activity of membrane-bound ion channels. This results in a net negative charge on the inside of the cell relative to the outside. This resting membrane potential can be locally depolarized under the influence of cell stimuli, leading to an inward current (bottom). **(b)** Schematic representation of the generation of a transepithelial potential (V_{TEP}) in human skin (individual cells in cornified layer and dermis are not shown). Selective, directional ion transport across the intact epithelium gives rise to a V_{TEP} that can be measured directly across the epithelium (top; 70 mV in this case). Tight junctions between epithelial cells (not shown) create physical connections between cells, providing high electrical resistance to the epithelial sheet. Wounding of an epithelial sheet results in collapse of the V_{TEP} at the wound (to 0 mV) without affecting the V_{TEP} distally (70 mV). Na^+ leaks out of the wound, resulting in an injury current toward the cut (thin arrows) and a lateral voltage gradient oriented parallel to the epithelial sheet (EF, electric field; thick arrows

at bottom). The wound site is the cathode of the electric field (bottom). [Bart Vanhaesebroeck 2006 Charging the batteries to heal wounds through PI3K. Nature Chem Biol. 2:9]

Pulsed Radio Frequency Device Innovation

The first PRFE device to be commercially developed in the 1950's was the Diapulse. These were large bulky clinic based PRFE devices as shown in figure 1A. Treatment regimens often consist of daily multiple 20 or 30 minutes treatments. Modern PRFE devices are smaller and more portable figure 1B, but still require mains power and still require daily treatment regimens. Despite the large number of clinical studies showing significant therapeutic effects (appendix table), the daily treatment regimens are a major handicap to the wide adoption of PRFE therapy as a postoperative treatment, injury recovery and an adjunct therapy for wound healing. Another obstacle to their wide adoption is the initial purchase costs which can range into thousands of dollars restricting home based use. Innovative research in the 1970's and 1980's by Dr. Bentall began to demonstrate that mains powered PRFE devices delivering relatively high energy treatments for short periods, could be replaced by extended time low energy treatments by portable wearable battery powered devices. This initial innovation and discovery led to the development of Bioelectronics range of wearable extended use PRFE devices with an example shown in figure 1C.

Figure 1. Shows a (A) Diapulse, (B) Provant Therapy System and (C) BioElectronics RecoveryRx, each device utilizes a 27.12MHz carrier frequency.

A. Diapulse	B. Provant Therapy System	C. BioElectronics RecoveryRx
A fixed clinic based PRFE device with a daily 2 x 30 min treatment regime	Suit case sized device offering portability with treatment regimens of 2x 30 min daily	Wearable PRFE device weighing 8g which operates for 1 week of continuous therapy
		

Extended treatment time Pulsed Radio Frequency Studies

The development of the Bioelectronics device was based on a pioneering work by Dr. Bentall. At the Proceeding of the 1st annual meeting of the Bioelectrical Repair and Growth Society. Dr. Bentall presented data comparing the effects of a 15 Watt pulsed radio frequency device at 27.12 MHz (Diapulse) to a 2 milliwatt pulsed device at 3 MHz on the tensile strength of rat abdominal wounds. Despite the large difference in the physical size and power output of the two devices, they showed a very similar profile in enhancing the tensile strength of the wounds. The 15 watt Diapulse treatment was given 3 x 20 min per day and the 2 milliwatt treatment was an overnight exposure, control was a 15 Watt light bulb. This was the first study to show that lower power with longer treatment duration was as effective as higher power shorter treatments. In unpublished studies on human experimental wounds, Bentall looked at full-thickness skin wounds 3 mm diameter on 20 patient volunteers. Ten patients received continuous radio frequency treatment, with a device powered by a 3.5 volt battery with a carrier frequency of 44 MHz, 100µsec pulse width and pulse frequency of 1 KHz. The observations from this study were that treatment of skin wounds with continuous pulsed radio frequency accelerated healing, and improved the histological appearance of the wounds.

Nicolle & Bentall (1982) published a pilot study with 21 patients on the use of a proprietary pulsed radio frequency energy device on the control of postoperative edema and bruising after blepharoplasty surgery. The initial published pilot results showed promising results. A larger patient set was assessed involving 61 patients, with results showing after 3 days of continuous (16 hrs/day) treatment a clear reduction in bruising and edema in patients who received pulsed radio frequency therapy.

Dr. Bentall published the following publication highlighting a number of pioneering studies using extended use pulsed radio frequency fields.

Bioelectrochemistry and Bioenergetics, 16 (1986) 531–548
 A section of *J. Electroanal. Chem.*, and constituting Vol. 212 (1986)
 Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

960 — LOW-LEVEL PULSED RADIOFREQUENCY FIELDS AND THE TREATMENT OF SOFT-TISSUE INJURIES *

R.H.C. BENTALL

Institute of Bioelectrical Research, Romanno Bridge, West Linton, Peeblesshire, EH46 7BY (Great Britain)

(Manuscript received April 19th 1986)

SUMMARY

The aim of this lecture is to outline the main physiological processes involved in the healing of wounds and to suggest a mechanism by which pulsed radiofrequency (RF) energy, or the currents induced in tissues by the application of that energy, may influence its course.

Emphasis is given to the part played by oedema in inhibiting the processes of wound healing. Reference is made to the growing evidence that pulsed RF energy affects the time course of wound healing and the hypothesis is proposed that one possible mechanism by which pulsed RF energy accelerates wound healing is by reducing oedema.

INTRODUCTION

Interest in the therapeutic potential of pulsed RF energy was stimulated following reports of bioelectric fields being associated with amphibian limb regeneration and bone mechanics [1–3]. It was at about the same time the first reports of the use of pulsed electromagnetic fields in relation to wound healing emerged [4–10].

Much of the initial work, particularly in the orthopaedic applications, was performed using direct current, pulsed direct current or alternating current, but more recently similar effect on bone healing have been demonstrated using pulsed electromagnetic field [11–13]. Watson [14] has reviewed bioelectrical effects in hard tissue applications and Frank and Szeto [15] have reviewed electromagnetically enhanced soft-tissue wound healing.

It was noted by Cameron [7] that pulsed radio frequency treatment of a surgical incision in the dog resulted in less severe oedema than in the untreated controls. If pulsed RF energy reduces oedema and so accelerates the preliminary stages of wound healing, it should also enhance the second and third phases. It is this hypothesis that has been investigated.

* Invited lecture delivered at the VIIIth International Symposium on Bioelectrochemistry and Bioenergetics, Bologna, June 24th–29th 1985.

Types of wound healing

Wound healing is usually divided into four main types according to the type of tissue involved and the nature and treatment of the wound [16]:

- (i) Primary wound healing — a soft-tissue wound closed by surgical procedure. This occurs in the vast majority of surgical wounds in which the edges of the wound are apposed.
- (ii) Secondary wound healing — a soft-tissue wound left to granulate as a means of closure. This occurs in wounds in which the edges are widely separated either as a deliberate surgical policy or as a consequence of tissue loss or destruction. This type of wound healing is most often encountered in pressure sores, leg ulcers and burn injuries.
- (iii) Hard tissue healing — the repair of fractures by bone regeneration. this will not be covered further.
- (iv) Healing in specialised tissues — lining epithelia and nerve tissue.

Phases of wound healing

The features of wound healing involve an acute inflammatory phase, a reparative phase, and a remodelling phase [17–20]. The time span for these events to take place can be measured in minutes and hours in the first phase, days to weeks in the second, and months to years for the third and final phase, at the end of which the wound is completely healed.

These three phases of wound healing consist principally of the following physiological events:

(a) The acute inflammatory reaction phase

- (i) Changes in vascular permeability.
- (ii) Appearance of fibrin.
- (iii) Infiltration of leucocytes and macrophages.
- (iv) Localised extravasation of blood.
- (v) Alteration in histamine and local hormone levels associated with bradykinins, prostaglandins and complement.

(b) The reparative phase

- (i) Decrease in local inflammatory reaction.
- (ii) Appearance of fibroblasts in the wound area.
- (iii) Associated production of collagen by the fibroblasts leading to increased wound tensile strength.
- (iv) Absorption of extravasated blood constituents.
- (v) Epithelial migration and basal cell mitotic activity.

(c) The remodelling phase

- (i) Longer period of slower collagen deposition.
- (ii) Crosslinking of collagen fibres.

- (iii) Repair of nerve endings.
- (iv) Formation of scar tissue.

In secondary wound healing the following additional events occur during the reparative phase:

- (i) Proliferation of capillary loops into the defect.
- (ii) Formation of granulation tissue in the area of tissue loss.
- (iii) Epithelial migration over the granulation tissue.
- (iv) Maturation of fibrous tissue from the granulation tissue.

A disadvantageous feature of secondary wound healing is that when the granulation tissue is resorbed it converts into massive fibrous tissue which leaves a puckered scar.

Factors affecting wound healing

There are many factors which influence the course of healing; the main factors of importance are listed below [18,21–25]:

- (i) Blood flow to the site of injury.
- (ii) Transport of oxygen to the wound.
- (iii) Oedema and inflammatory reaction in the wound.
- (iv) Nutritional status (Vitamin A, B, C and D, zinc and proteins are all essential).
- (v) Underlying pathologies, *e.g.* renal failure, diabetes mellitus.
- (vi) The effects of some drugs, *e.g.* steroids.

Wound healing and oedema

Blood flow and hence the transport of oxygen to the wound is of paramount importance in the normal sequence of healing. Respiratory uptake of oxygen by haemoglobin in red blood cells occurs in alveoli in the lungs. It is then transported in the peripheral circulation to capillaries in the tissues. Oxygen diffuses out of the capillaries, through the interstitial spaces and into the cells. The rate of diffusion depends upon the oxygen tension gradient across the interstitial space and the overall distance between the capillaries and the cells [22,26].

Oedema is an accumulation of fluid in the interstitial spaces between the cells [27]; it is the cause of swelling and, in the case of a surgical wound, may cause visible tension around the suture line [28]. Oedema occurs during the inflammatory reaction phase of wound healing as a result of changes in microvascular permeability [29].

In Sevitt's classic work in 1958 [30] he described the cycle of events following burn injury which leads to tissue necrosis. He pointed out that oedema reduces the perfusion pressure by raising the pressure within the tissue. Oedema occludes the capillaries at the site of the wound and thereby prevents the flow of blood. This in turn reduces the supply of oxygen to the cells [31]. In addition, the accumulating oedema between the cells and the capillaries increases their physical separation

which slows oxygen diffusion from the capillaries to the cells. This view is supported by the work of Remensnyder [32] demonstrating that steep oxygen gradients exist over very short distances surrounding a 1 mm burn of the rat cremaster. Moreover, he showed that the hypoxic areas of the wounds corresponded to the observable areas of vascular stagnation and thrombus formation.

The influence of oedema is not limited to the inflammatory phase of wound healing. For example, Speer [33], using a primary wound healing model, demonstrated a significantly lower tensile strength in the portion of a wound which had been associated with relatively severe oedema. He also documented evidence that the oedematous areas of the wound showed relatively slow afferent and efferent microcirculation compared with the non-oedematous areas. It seems likely that the dynamics of the microcirculation is altered by oedema. The destructive inflammatory phase of wound healing is thus prolonged, resulting in the delayed onset of the collagen synthesis phase of wound healing [34].

This concept of a prolonged inflammatory phase of wound healing is supported by the demonstration [29] that low tissue oxygen tension (indirectly caused by oedema) may be responsible for increased capillary permeability. The existing interstitial oedema is thus further compounded.

In conclusion, oedema exerts three detrimental effects during the inflammatory phase of wound healing:

- (i) Stagnation due to increased tissue tension.
- (ii) Increased distance for oxygen diffusion.
- (iii) Increased permeability of the capillaries.

These effects interact to delay the onset of collagen production which, in turn, delay the development of tensile strength of the wound.

TENSILE STRENGTH OF RAT ABDOMINAL WOUNDS

Introduction

The effect of pulsed RF energy on the development of tensile strength of a wound was investigated in a laboratory animal model. The purpose of this study was to compare, at two time intervals following surgery (2 days and 8 days), the tensile strength of rat abdominal wounds treated with one of two pulsed radio-frequency devices (15 W or 2 mW nominal output) compared with a placebo equivalent (15 W light bulb).

Method

110 Wistar rats (200 grams) were used in this study. Under ether anaesthesia a 2.5 cm transverse incision was made in the abdominal wall through to the peritoneal cavity of each rat. The wounds were closed with five interrupted silk sutures through all layers and the rats were randomly assigned to one of three treatment groups: 15 W, 2 mW or placebo.

The daily treatment regimen for each of the groups respectively was three episodes of 20 min exposures to the 15 W device, overnight exposure to the 2 mW device, or three episodes of 20 min exposure to the 15 W light bulb. Treatment continued until the randomised sacrifice of each animal at two or eight days post-operatively.

Prior to sacrifice each rat was anaesthetised, a plastic bag was inserted into its peritoneal cavity and its sutures were removed. The bag was progressively inflated with water at a constant rate until the wound ruptured. The pressure of water in the bag was recorded continuously to determine the resistance of the wound to increasing intra-abdominal pressure.

Device specifications

- (i) Placebo device - 15 W light bulb.
- (ii) 15 W pulsed RF device:

Nominal power output	15 W
Carrier frequency	27 MHz
Pulse width	65 μ s
Pulse repetition frequency	200 Hz

- (iii) 2 mW pulsed RF device:

Nominal power output	2 mW
Carrier frequency	3 MHz
Pulse width	100 μ s
Pulse repetition frequency	1 kHz

Results

The profiles of the tracings of pressure against time were different at the two different time intervals. Two days after incision the wounds were still quite weak and there was a single point at which each wound completely broke down. Eight days after incision there was a biphasic response. A first pressure peak was reached when the fascia ruptured, allowing the bag to spread out and the water pressure to drop. A second peak was then reached when the skin itself parted.

Three separate methods were used to quantify the tensile strength of the wounds:

- (i) End volume — the total volume of water infused into the bag when the wound burst. This value was extremely variable at eight days and is not reported.
- (ii) Area under the graph — this integrates the time period (seconds) over which pressure of water (mm Hg) was withstood and hence allows for different sized peritoneal cavities and for differences in the extent to which the bags spread out.
- (iii) Wound index (8 day groups only) — this is the sum of the two pressure peaks multiplied by the time difference (in seconds) between them.

TABLE 1

Tensile strength of rat abdominal wounds at two and eight days following transverse surgical incision

	2 DAY			8 DAY		
	value	% increase	p value	value	% increase	p value
<i>Placebo groups</i>						
<i>n</i> = 25						
End volume	97.7	—	—	—	—	—
Area under graph	1777.2	—	—	13116.4	—	—
Wound index	N/A	—	—	10563.4	—	—
<i>15 W groups</i>						
<i>n</i> = 25						
End volume	112.7	15.4	0.025	—	—	—
Area under graph	2252.2	26.7	0.025	20642.5	57.4	0.025
Wound index	N/A	—	—	17563.4	66.3	0.01
<i>2 mW groups</i>						
<i>n</i> = 5						
End volume	113.6	16.5	0.025	—	—	—
Area under graph	3256.6	83.2	0.01	13910.0	1.1	NS
Wound index	N/A	—	—	15287.0	44.7	0.01

T tests were used to compare the experimental groups with the placebo groups and the results are shown in Table 1.

Conclusions

These results clearly show that pulsed radiofrequency energy from both these devices does have a significantly effect on the tensile strength of rat abdominal wounds.

Despite the gross differences in the physical size and power output of the two devices (15 W and 2 mW), they showed a very similar profile of activity in enhancing the development of tensile strength. This confirms that the effect of pulsed radio frequency energy on wound healing is not thermal in origin.

HUMAN EXPERIMENTAL SKIN WOUNDS

Introduction

If an effect of pulsed RF energy on oedema leads to improved oxygen supply and the earlier appearances of the reparative events of the second phase of wound healing, its beneficial properties will not be confined to primary wound healing.

Two double-blind experiments were performed to determine the effect of treatment with pulsed RF fields on the histological appearance of repaired human full-thickness punch wounds of the skin of the lower limbs. This is a secondary

wound healing model which permits good experimental control. The first experiment sought to establish whether any effect of pulsed RF field could be observed.

The purpose of the second experiment was to investigate at what point in time the thickened epithelium observed in the first study developed, and to obtain histological evidence confirming that the events of the reparative phase of wound healing occur earlier in the treated wounds.

Method

Experiment 1: A full-thickness disc of skin (2 cm diameter) was removed from each inner calf of a human volunteer. Each wound was allocated an identical treatment device, one active and the other placebo. The identity of the device was revealed only when the wounds had completely healed. The devices were worn for 16 h a day until that time. Biopsies of both wounds were performed nine months after healing. The tissue was sectioned and stained with either Haematoxylin + Eosin or Van Gieson. The sections were examined by a histopathologist who was not aware which wound had been actively treated.

Experiment 2: In this double-blind experiment, a series of twenty (3 mm diameter) full-thickness wounds were made on the upper aspect of the thighs of a human volunteer. Ten wounds received placebo treatment, the other ten received active treatment. The pulsed RF devices were similar to the lower power devices used in the rat tensile strength experiment and were worn continuously. Biopsies of the wounds were performed during the initial period of healing, at 1, 2, 3, 5, 7, and 14 days. The results shown below are a summary of all of time groups.

Device specification

Power source	3.5 V battery
Carrier frequency	44 MHz
Pulse width	100 μ s
Pulse repetition frequency	1 kHz

Results

Experiment 1:

The placebo side was characterised by a thin epidermal layer (see Fig. 1, side B) and showed other features of normal secondary wound healing:

- (i) Basal epidermal layer pleomorphism.
- (ii) Lack of pallisading.
- (iii) Endarteritis.

The placebo-treated wound took 54 days to heal.

In contrast, the actively treated wound showed an almost normal depth of

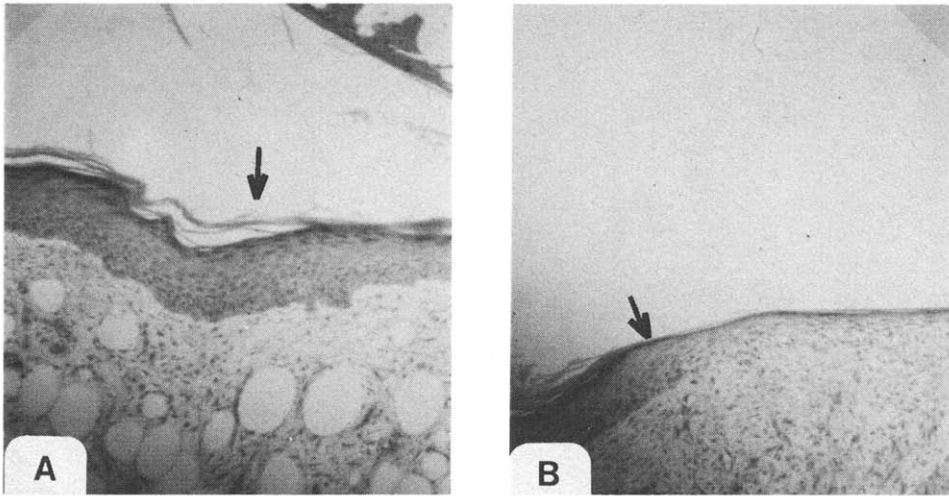


Fig. 1. Epidermal layer of repaired human punch skin wound. (A) Actively treated wound; (B) placebo-treated wound. (Arrows indicate the wound edges.)

epidermal layer (see Fig. 1, side A) and other advantageous features not usually associated with secondary wound healing:

- (i) No pleomorphin.
- (ii) Basal cell pallisading.
- (iii) No endarteritis, but developed endothelium.

The actively treated wound took 39 days to heal.

Experiment 2:

As with the first experiment the placebo-treated wounds showed the typical features of secondary wound healing:

- (i) Thin epidermia.
- (ii) Basal-layer pleomorphism.

The actively treated wounds showed evidence of:

- (i) Earlier epidermal budding.
- (ii) Earlier migration into the wound.
- (iii) Earlier appearance of rete ridges.
- (iv) Almost normal depth of final epidermis.

Conclusions

Treatment of skin wounds with pulsed radio-frequency energy 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.

MENINGOMYELOCELE STUDY

Introduction

A meningomyelocele is a hernial protrusion of the meninges and spinal cord roots through a bony defect in the vertebral column. Some infants are born with this condition, requiring surgical closure of the defect within the first few days of life. One of the complications of the procedure is dehiscence of the wound (due to the tension of the skin across the operative site). The meninges may become exposed, thus providing a route for infection which may lead to ascending meningitis. This can end in mortality.

The purpose of this study was to determine the effects of pulsed RF energy on the integrity of surgical closure of this defect. If treatment with pulsed RF fields leads to a reduction in oedema then tissue tension would be lower and there would be a reduced likelihood of the wounds breaking down.

Method

A prospective study was started in 1974. It ran for seven years and involved 90 patients. The surgical procedure was performed by the same surgeons throughout the duration of the study. This study was not double-blind, a retrospective study of the previous 470 cases performed in the unit confirmed a wound breakdown rate of 7%. The pulsed RF devices were placed over the wound dressings post-operatively and treatment lasted for 16 h a day until four weeks after surgery.

Written assessments of all the wounds were completed daily and photographic confirmation of the post-operative course of some wounds was collected by ward staff. Neurological status was assessed by physiotherapists before and after surgery and at regular intervals thereafter.

Device Specifications

Specifications for the device used in this study are not available.

Results

In the first 90 patients entered into the study, the incidence of wound breakdown was significantly reduced from 7% to 0% ($\chi^2 = 6.67$, $p = 0.01$).

Conclusions

Wound breakdown following meningomyelocele closure with its attendant risk of ascending meningitis was eliminated. There were no obvious alterations in surgical

technique or in post-operative care that might have accounted for the reduction in wound breakdown.

These results suggest a considerable benefit to be derived from treatment with pulsed RF energy and clearly warrant further investigations under double-blind conditions.

BLEPHAROPLASTY STUDY

Introduction

The surgical procedure of blepharoplasty may be performed under general or local anaesthesia and involves removal of excess skin and fat from the upper and/or lower eyelids. The low tension in the skin of the peri-orbital region means that post-operative oedema and bruising are inevitable. It is an ideal clinical model for double-blind evaluation of pulsed RF treatment because it provides asymptomatic patients who each undergo a bilateral procedure performed by a single surgeon; the patient acts as his or her own control.

A double-blind pilot study has been reported previously [35]. In the pilot study no attempt was made to obtain any numerical estimates of oedema and bruising on which to perform statistical analysis. The purpose of the present study was to replicate the clinical effect observed in the pilot study and to quantify that effect using a larger sample of patients.

Method

The subjects of this clinical study were the patients of a plastic surgeon (Mr. F.V. Nicolle) practising in London, England. All patients attending for bilateral blepharoplasty who gave their informed consent to participation were entered into the study; there were no specific exclusion criteria. Patients receiving surgery to the upper lids and/or the lower lids were included.

Patients were randomly assigned a pair of special lensless spectacles to provide treatment to the lids of one eye but not the other. Active and placebo antennae were fitted into the light weight spectacle frames and electrical components were housed in one leg of the frames. The placebo antenna was electrically shielded to prevent re-radiation from the active antenna which emitted pulsed RF energy of the following specifications:

Nominal power output	73 μ W
Carrier frequency	26 MHz
Pulse width	73 μ s
Pulse repetition frequency	900 Hz

Patients therefore acted as their own control and they were not aware which eye received treatment. Treatment commenced immediately following surgery and the patients were instructed to wear the spectacles for 16 h per day for the following

three days. Apart from this no modifications were made to the normal post-operative care of the patients. Patients were asked to keep a log, on a small card provided, of the hours for which they wore the spectacles.

At each post-operative visit, that is at one day (a few cases only) and at three, four or five days after surgery, the nurse took a clinical photograph which was developed into a colour slide. The clinical logistics of the study precluded the taking of absolutely standard photographs. Therefore, in order to be able to make a correction to the measurements for the absolute size of each photograph, it was decided to place a centimetre scale reference sticker on the forehead of each patient prior to the clinical photograph being taken. Unfortunately this decision was not taken until after the first twelve patients had been entered into the study.

Measurements

The slides were used to obtain measurements of bruising and the amount each eye was open and they were also clinically assessed by a panel of three judges (one surgeon, one nurse and one lay person).

The bruising beneath each eye was recorded by projecting the slide onto a piece of acetate film and then drawing a planimetric trace of the bruised regions below the median palpebral tissue on each side. Only the areas of clearly defined red or purple bruising were included, not the rather diffuse areas of yellow. A System III Image Analysis Machine (AMS Limited) was then used to measure the area (in square centimetres) of the planimetric trace beneath each eye.

The slides were then projected onto a white piece of paper on which two thin black "+" signs had been drawn. The height of the palpebral fissure of each eye (at the point of bisection of the pupil) and the size of the centimetre scale reference sticker (when present) were marked off on the "+" signs with a thin pencil. The paper was then laid flat to enable the amount each eye was open and the length of the scale reference sticker to be measured with a ruler.

To obtain ratings of the extent of oedema, bruising and scleral haemorrhage, the three assessors examined the projected slides and recorded a rating of each clinical sign on a specially prepared form. The eyes were rated on the following scale for each sign:

2R The patient's RIGHT eye shows *significantly less* - - - - - than the patient's LEFT eye.

1R The patient's RIGHT eye shows less - - - - - than the patient's LEFT eye but this is of *little clinical significance*.

0 There is no discernable difference between the patient's LEFT and RIGHT eyes with respect to - - - - -.

2L The patient's LEFT eye shows *significantly less* - - - - - than the patient's RIGHT eye.

1L The patient's LEFT eye shows less - - - - - than the patient's RIGHT eye but this is of *little clinical significance*.

All of the Day 3 (4 or 5) photographs were assessed before any of the Day 1

photographs and the three assessors were blind as to the side of treatment of each patient.

Analyses

Bruising and eye-opening data were analysed using related samples *t* tests and contingency tables were drawn up of the clinical assessment data and submitted to χ^2 tests of association.

Patients who failed to return the log of the times the spectacles had been worn or who wore the spectacles for fewer than 8 h per day for at least two days were excluded from the analysis.

Because not all of the pictures were taken with the patients wearing a scale reference sticker it was not possible to provide a correction factor to the measurement data in every case. Two analyses were therefore performed. To include all patients, the data was transformed to the percentage of total bruising or eye opening

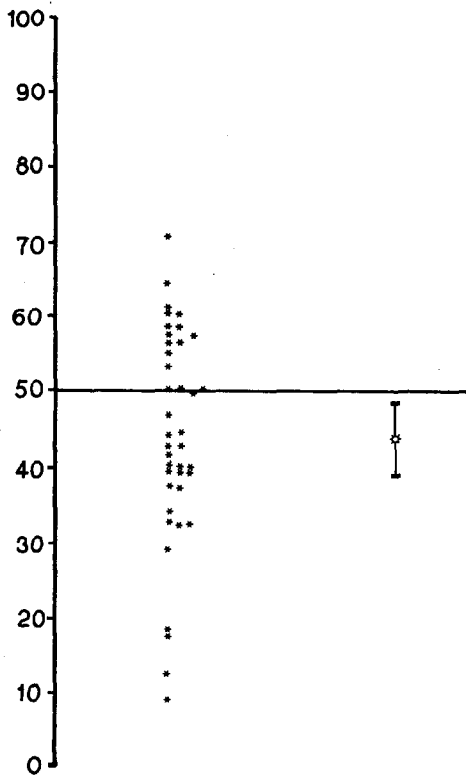


Fig. 2. Percentage of total bruising which was on the active side (Day 3, 4 or 5 post-operatively). Graph shows individual score for each patient and the group mean ($\pm 95\%$ confidence intervals).

which was on the active side. The second analysis, which used the measured size of the scale reference sticker to convert the bruising data to actual areas, is considered to give a more meaningful picture even though it included fewer patients.

Results

There were a total of sixty patients available for analysis in the present study. Two of these patients failed to return the log of the times when the spectacles were worn, two had worn the spectacles for fewer than the required 2 days and fourteen had worn the spectacles for fewer than the required 8 h per day. There were thus forty-two patients entered into the analyses, of whom nine patients had slides from Day 1 Post-operation and of these two had slides from Day 1 only.

Figure 2 shows the area of bruising on the actively treated side as a percentage of the total bruising of both sides. It can be seen that for the patients as a whole the percentage of the total bruising which was on the active side was significantly less

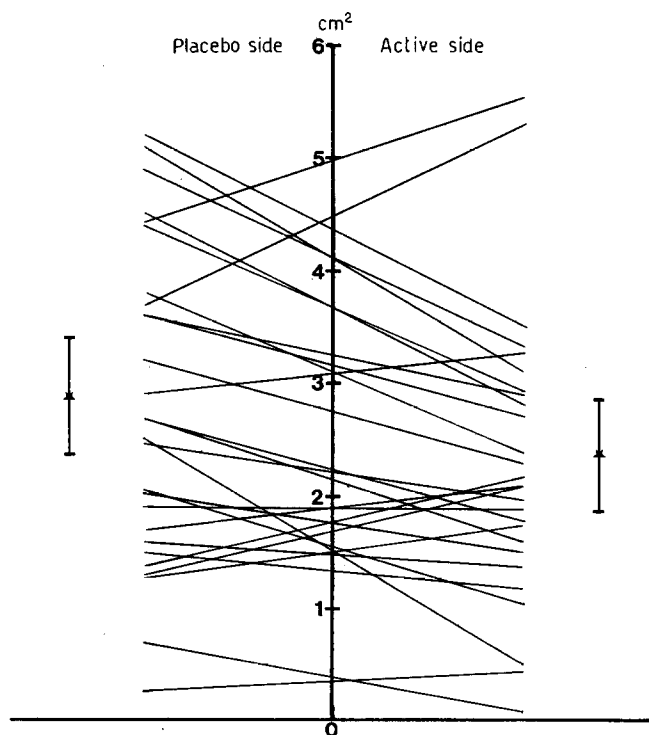


Fig. 3. Actual areas of bruising on the actively treated side and the placebo side (Day 3, 4 or 5 post-operatively). Graph shows the scores for each patient and the group means ($\pm 95\%$ confidence intervals).

than 50%, which is the outcome which would be expected to occur by chance ($t = 2.56$, $p = 0.015$). This is equivalent to a mean reduction in bruising on the active side of 20.7% (95% confidence interval, 5.2% to 33.8%).

For the 28 patients who had worn the scale reference sticker it was possible to convert the bruised area measurements to actual areas. Figure 3 shows these results. It can be seen that the mean area of bruising on the placebo side was 2.88 cm² and for the active side it was 2.38 cm². This difference was again statistically significant ($t = 2.47$, $p = 0.02$) and indicates that there was 17.4% less bruising on the actively treated side (95% confidence interval, 3.7% to 31%).

Figures 4 and 5 show, for the Day 1 and Day 3, 4 or 5 photographs respectively, the height of the palpebral fissure of the actively treated side as a percentage of the

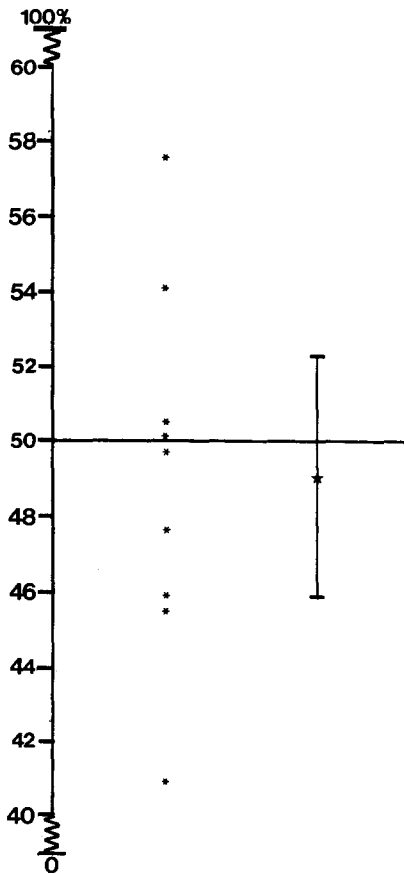


Fig. 4. Height of the palpebral fissure on the active side as a percentage of the combined height of the fissure of both eyes (Day 1 post-operatively). Graph shows individual score for each patient and the group mean ($\pm 95\%$ confidence intervals).

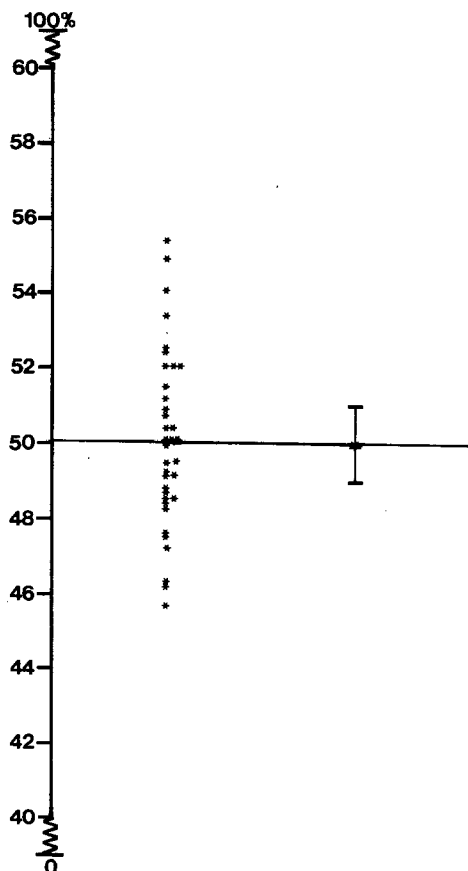


Fig. 5. Height of the palpebral fissure on the active side as a percentage of the combined height of the fissure of both eyes (Day 3, 4 or 5 post-operatively). Graph shows individual score for each patient and the group mean ($\pm 95\%$ confidence intervals).

combined heights of the palpebral fissures of both sides. In neither case is this value significantly different from 50% (Day 1: $t = 0.52$, NS; Day 3, 4 or 5: $t = 0.62$, NS).

Although the clinical sign of oedema is more striking on the first day following surgery, too few patients with Day 1 photographs were available to permit a meaningful analysis of the clinical assessments of them. Even for the Day 3, 4 or 5 photographs there were not sufficient patients to perform a reliable analysis of the full five assessment levels. However, by combining the two levels of assessment on each side (2R and 1R, and 2L and 1L) and excluding the small number of cases assessed as showing no difference, the cell entries are large enough to permit meaningful conclusions (see Table 2). It can be seen that there is a strong

TABLE 2

Clinical assessment of oedema by surgeon assessor (Table combining assessment levels)

	Less oedema on left	Less oedema on right	Total
Left side active	12	5	17
Right side active	5	13	18
Total	17	18	35
Statistic	Value	D.F.	Probability
Pearson χ^2	6.4	1	0.01

association between the clinical assessments made and the side of activity of the spectacles that the patient was wearing (Pearson $\chi^2 = 6.4$, $p = 0.01$).

Table 3 similarly shows the same surgeon's assessments of the patients' bruising. Again the association between assessments made and side of activity of the spectacles worn is statistically significant (Pearson $\chi^2 = 5.9$, $p = 0.015$).

Only six patients show any scleral haemorrhage and there is no evidence of its presence being associated with the side of activity of the spectacles being worn (Pearson $\chi^2 = 1.3$, NS).

The results of the other two assessors were in broad agreement with the findings of the surgeon, though, with more assessments being recorded as *no discernable difference*, the same levels of significance were not attained.

Discussion

The results of the present study provide objective evidence for and statistical underpinning of the clinical impressions reported in the pilot study. After approximately three days of post-operative treatment with low levels of pulsed RF energy there is a clear reduction in the area of bruising and in the observable signs of oedema around the treated eye in comparison with the untreated eye.

TABLE 3

Clinical assessment of bruising by surgeon assessor (Table combining assessment levels)

	Less bruising on left	Less bruising on right	Total
Left side active	12	4	16
Right side active	6	12	18
Total	18	16	34
Statistic	Value	D.F.	Probability
Pearson χ^2	5.9	1	0.015

GENERAL DISCUSSION

Four studies have been described which provide support, from both laboratory and clinical research environments, for the contention that pulsed RF fields may be of value in the treatment of soft tissue-injuries. Furthermore, the hypothesis that such effects may be mediated through a reduction in oedema has been upheld. As argued in the introduction, the influence of oedema, which occurs during the inflammatory reaction phase of wound healing, may extend beyond this phase and result in lower wound tensile strength and delay the onset of collagen synthesis [34]. The laboratory study of rat abdominal wound repair has indeed demonstrated that tensile strength is more developed in the groups treated with pulsed RF energy. Further evidence that the physiological events of the reparative phase of wound healing occur earlier following treatment with pulsed RF fields was found in the human skin wound experiments; the first experiment showed an improved end result and in the second experiment histological evidence of repair appeared earlier in the treated wounds. That these effects were not confined to the laboratory setting was demonstrated in the meningomyelocele study in which wound breakdown following surgery was eliminated. This might have been due to improved tensile strength of the wound or to a reduction in oedema creating a lower bursting pressure (or both), although it must be stressed that this was not a randomized control trial. Finally, in the blepharoplasty study direct evidence has been obtained that pulsed RF treatment reduces both bruising and oedema. Oedema is produced by changes in microvascular permeability, by the breakdown of extravasated proteins (which increases tissue osmotic pressure), by increased capillary blood pressure and by increased fluidity of the tissue ground substance (preventing the rise in tissue tension which opposes further release of exudate) [25]. One possible mechanism of action of the pulsed RF fields might be to prevent the disaggregation of the mucopolysaccharides of ground substance which causes its increased fluidity and is one of the earliest features of the inflammatory response. In this way the fluid exudate and free red blood cells from the damaged capillaries would be less able to spread from the initial site of injury. It is interesting in this context to note that attempts to model the effects of electric fields on connective tissue [36] have concentrated on the polysaccharides (GAGs) which are the main charge-bearing constituents.

CONCLUSIONS

The body of research into the effects of treatment of wounds with pulsed RF fields has demonstrated:

- (i) Earlier appearance of tensile strength.
- (ii) Evidence of earlier onset of reparative processes in secondary wound healing.
- (iii) Reduced bruising and oedema in primary wound healing.

It may therefore be concluded that treatment with pulsed RF or similarly configured devices can accelerate some processes of primary and secondary wound

healing. It is not proven that these effects are mediated through a reduction of interstitial oedema; there may be a number of separate mechanisms involved.

REFERENCES

- 1 E. Fukada and I. Yasuda, *J. Phys. Soc. Jpn.*, 12 (1957) 1158.
- 2 R.O. Becker, *Science*, 134 (1961) 101.
- 3 C.A.L. Bassett and R.O. Becker, *Science*, 137 (1962) 1063.
- 4 R.H.C. Bentall, *Br. J. Cancer*, 45 (1982) Suppl. V, 82.
- 5 R.H.C. Bentall in *Charge and Field Effects in Biosystems*, M.J. Allen and P.N.R. Usherwood (Editors), Abacus Press, Kent, 1984, pp. 331–351.
- 6 M. Nadashi, *Am. J. Orthop.*, 2 (1960) 105.
- 7 B.M. Cameron, *Am. J. Orthop.*, 3 (1961) 336.
- 8 B.M. Cameron, *Am. J. Orthop.*, 6 (1964) 72.
- 9 J.E. Fenn, *Can. Med. Assoc. J.*, 100 (1969) 251.
- 10 J.H. Goldin, N.R.G. Broadbent, J.D. Nancarrow and T. Marshall, *Br. J. Plast. Surg.*, 34 (1981) 267.
- 11 C.A.L. Bassett, R.J. Pawluk and A.A. Pilla, *Science*, 184 (1974) 575.
- 12 J. Watson and E.M. Downes, *Med. Biol. Eng. Comput.*, 17 (1979) 161.
- 13 C.A.L. Bassett, S.N. Mitchell and S.R. Gaston, *J. Bone Jt. Surg.*, 63A (1981) 511.
- 14 J. Watson, *Proc. IEEE*, 67 (1979) 1339.
- 15 C.B. Frank and A.Y.J. Szeto, *IEEE Eng. Med. Biol.*, 12 (1983) 27.
- 16 A.J.H. Rains and H.D. Ritchie in *Bailey and Love's Short Practice of Surgery*, H.K. Lewis, London, 1977.
- 17 R. Marks in *Tissue Repair and Regeneration*, L.E. Glynn (editor), Elsevier/North Holland Biomedical Press, Amsterdam, 1981, pp. 309–342.
- 18 J.F. Newcombe in *Scientific Basis of Surgery*, W.T. Irvine (Editor), Churchill Livingstone, London, 1972, pp. 433–456.
- 19 P. Pullar in *Modern Trends in Forensic Medicine*, K.A. Mant (Editor), Butterworths, London, 1973, Vol. 3, pp. 64–92.
- 20 G.B. Ryan and G. Majno, *Am. J. Pathol.*, 86 (1977) 185.
- 21 J.E. Dunphy and K.N. Udupa, *N. Engl. J. Med.*, 253 (1955) 847.
- 22 T.K. Hunt, *World, J. Surg.*, 4 (1980) 271.
- 23 L.E. King, *J. Invest. Dermatol.*, 84 (1985) 165.
- 24 D. Montandon, G. D'Andrian and G. Gabbiani, *Clin. Plast. Surg.*, 4 (1977) 325.
- 25 J.B. Walter and M.S. Israel in *General Pathology*, 3rd ed., Churchill Livingstone, London, 1972, pp. 167–189.
- 26 C.A. Keele and E. Neil, *Samson Wright's Applied Physiology*, Oxford University Press, London, 1971.
- 27 A. Leaf, *Circulation*, 48 (1973) 455.
- 28 M.A. Shields and H.A.F. Dudley, *Br. J. Surg.*, 158 (1971) 598.
- 29 E.M. Landis, *Ann. N. Y. Acad. Sci.*, 46 (1946) 713.
- 30 S. Sevitt, *J. Pathol. Bacteriol.*, 75 (1958) 27.
- 31 S. Sevitt, *J. Pathol. Bacteriol.*, 61 (1949) 427.
- 32 J.P. Remensnyder, *Arch. Surg.*, 105 (1972) 477.
- 33 D.P. Speer, *J. Surg. Res.*, 27 (1979) 385.
- 34 E.E. Peacock and W. Van Winkle, *Wound Repair*, Saunders, Philadelphia, 1976, pp. 1–21, 145–02, 215–231.
- 35 F.V. Nicole and R.H.C. Bentall, *Aesthet. Plast. Surg.*, 6 (1982) 169.
- 36 A.J. Grodzinsky, *CRC Crit. Rev. Biomed. Eng.*, 9 (1983) 133.

Confirming Animal Studies

In 2011 a significant study* on the healing of wounds in diabetic mice confirmed the initial finding of Dr. Bentall on experimental wounds in humans and rats. In this recent study full-thickness cutaneous wounds were made in db/db mice (diabetic mouse model), with one group treated with PRFE and a sham treated control group. The PRFE treatment was delivered by a higher power device twice daily for 30 min. However, detailed analysis of the wounds showed the treated group had accelerated wound healing through wound contraction via stimulating cell proliferation, granulation tissue formation and collagen deposition. These studies confirm the findings outlined by Dr. Bentall on wound healing and show that PRFE promotes wound healing, but that extended time PRFE treatments and higher power short time PRFE treatments, have the same impact on healing of full thickness cutaneous wounds.

* Qin Li, , Huangkai Kao, Evan Matros, , Cheng Peng, George F. Murphy, Lifei Guo. Pulsed Radio Frequency Energy (PRFE) Accelerates Wound Healing In Diabetic Mice *Plast Reconstr Surg*. 2011 Jun;127(6):2255-62.

Extended time low power clinical studies

The studies by Dr. Bentall laid the ground work for further development of PRFE device that are small portable and offer a significant therapeutic benefit. The studies below were carried by a variety of extended use PRFE devices. Titles and abstracts are shown:

Frederick V. Nicolle, M. Chir. and Richard M. Bentall Use of Radio-Frequency Pulsed Energy in the Control of Postoperative Reaction in Blepharoplasty *Aesth. Plast. Surg.* 6:169-171, 1982

This is a preliminary report of the use of a device to apply small pulses of radio-frequency energy to surgical wounds in order to improve wound healing. The device was applied to one eye in 21 patients who underwent bilateral blepharoplasty. There were no device related complications. In 11 patients, edema and ecchymosis were noticeably less on the treated side within 24 hours of surgery. In 6 patients, ecchymosis and swelling were so slight that no difference between treated and untreated sides was visible. Two patients were noticeably worse on the treated side. Further studies will be conducted.

Foley-Nolan D, Moore K, Codd M, Barry C, O'Connor P, Coughlan RJ. Low energy high frequency pulsed electromagnetic therapy for acute whiplash injuries. A double blind randomized controlled study. *Scand J Rehabil Med.* 1992;24(1):51-9.

The standard treatment of acute whiplash injuries (soft collar and analgesia) is frequently unsuccessful. Pulsed electromagnetic therapy PEMT (as pulsed 27 MHz) has been shown to have pro-healing and anti-inflammatory effects. This study examines the effect of PEMT on the acute whiplash syndrome. One half of the 40 patients entering the study received active PEMT collars: the other half facsimile (placebo). All patients were given instructions to wear the collar

for eight hours a day at home and advised to mobilise their necks. At 2 and 4 weeks the actively treated group had significantly improved (p less than 0.05) in terms of pain (visual analogue scale). By chance movement scores for the PEMT group were significantly worse at entry to the study than the control group (p less than 0.05). At 12 weeks they had become significantly better (p less than 0.05). PEMT as described is safe for domiciliary use and this study suggests that PEMT has a beneficial effect in the management of the acute whiplash injury.

Foley-Nolan D, Barry C, Coughlan RJ, O'Connor P, Roden D Pulsed high frequency (27MHz) electromagnetic therapy for persistent neck pain. A double blind, placebo-controlled study of 20 patients. Orthopedics. 1990 Apr;13(4):445-51.

In the majority of patients with neck pain, symptoms will resolve spontaneously or quite quickly in response to therapy. However, some patients' symptoms persist for a long period, irrespective of therapy. In this study, 20 patients with persistent (greater than 8 weeks) neck pain were enrolled in a double blind, placebo-controlled trial of low energy, pulsed electromagnetic therapy (PEMT)--a treatment previously shown to be effective in soft tissue injuries. For the first 3-week period, group A (10 patients) received active PEMT units while group B (10 patients) received facsimile placebo units. After 3 weeks, both pain (visual analogue scale (P less than .023) and range of movement (P less than .002) had improved in the group on active treatment compared to the controls. After the second 3 weeks, during which both groups used active units, there were significant improvements in observed scores for pain and range of movement in both groups. PEMT, in the form described, can be used at home easily in the treatment of patients with neck pain. It is frequently successful and without side effects.

Stiller MJ, Pak GH, Shupack JL, Thaler S, Kenny C, Jondreau L. A portable pulsed electromagnetic field (PEMF) device to enhance healing of recalcitrant venous ulcers: a double-blind, placebo-controlled clinical trial. Br J Dermatol. 1992 Aug;127(2):147-54.

A prospective, randomized, double-blind, placebo-controlled multicenter study assessed the clinical efficacy and safety of pulsed electromagnetic limb ulcer therapy (PELUT) in the healing of recalcitrant, predominantly venous leg ulcers. The portable device was used at home for 3 h daily during this 8-week clinical trial as an adjunct to a wound dressing. Wound surface area, ulcer depth and pain intensity were assessed at weeks 0, 4 and 8. At week 8 the active group had a 47.7% decrease in wound surface area vs. a 42.3% increase for placebo ($P < 0.0002$). Investigators' global evaluations indicated that 50% of the ulcers in the active group healed or markedly improved vs. 0% in the placebo group, and 0% of the active group worsened vs. 54% of the placebo group ($P < 0.001$). Significant decreases in wound depth ($P < 0.04$) and pain intensity ($P < 0.04$) favoring the active group were seen. Patients whose ulcers improved significantly after 8 weeks were permitted to continue double-blind therapy for an additional 4 weeks. Eleven active and one placebo patient continued therapy until week 12, with the active treatment group continuing to show improvement. There were no reports of adverse events

attributable to this device. We conclude that the PELUT device is a safe and effective adjunct to non-surgical therapy for recalcitrant venous leg ulcers.

Hedén P, Pilla AA. Effects of pulsed electromagnetic fields on postoperative pain: a double-blind randomized pilot study in breast augmentation patients. *Aesthetic Plast Surg.* 2008 Jul;32(4):660-6.

Postoperative pain may be experienced after breast augmentation surgery despite advances in surgical techniques which minimize trauma. The use of pharmacologic analgesics and narcotics may have undesirable side effects that can add to patient morbidity. This study reports the use of a portable and disposable noninvasive pulsed electromagnetic field (PEMF) device in a double-blind, randomized, placebo-controlled pilot study. This study was undertaken to determine if PEMF could provide pain control after breast augmentation. Forty-two healthy females undergoing breast augmentation for aesthetic reasons entered the study. They were separated into three cohorts, one group (n = 14) received bilateral PEMF treatment, the second group (n = 14) received bilateral sham devices, and in the third group (n = 14) one of the breasts had an active device and the other a sham device. A total of 80 breasts were available for final analysis. Postoperative pain data were obtained using a visual analog scale (VAS) and pain recordings were obtained twice daily through postoperative day (POD) 7. Postoperative analgesic medication use was also followed. VAS data showed that pain had decreased in the active cohort by nearly a factor of three times that for the sham cohort by POD 3 ($p < 0.001$), and persisted at this level to POD 7. Patient use of postoperative pain medication correspondingly also decreased nearly three times faster in the active versus the sham cohorts by POD 3 ($p < 0.001$). Pulsed electromagnetic field therapy, adjunctive to standard of care, can provide pain control with a noninvasive modality and reduce morbidity due to pain medication after breast augmentation surgery.

Rohde C, Chiang A, Adipoju O, Casper D, Pilla AA. Effects of pulsed electromagnetic fields on interleukin-1 beta and postoperative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients. *Plast Reconstr Surg.* 2010 Jun;125(6):1620-9.

Surgeons seek new methods of pain control to reduce side effects and speed postoperative recovery. Pulsed electromagnetic fields are effective for bone and wound repair and pain and edema reduction. This study examined whether the effect of pulsed electromagnetic fields on postoperative pain was associated with differences in levels of cytokines and angiogenic factors in the wound bed. In this double-blind, placebo-controlled, randomized study, 24 patients, undergoing breast reduction for symptomatic macromastia received pulsed electromagnetic field therapy configured to modulate the calmodulin-dependent nitric oxide signaling pathway. Pain levels were measured by a visual analogue scale, and narcotic use was recorded. Wound exudates were analyzed for interleukin (IL)-1 beta, tumor necrosis factor-alpha, vascular endothelial growth factor, and fibroblast growth factor-2. Pulsed electromagnetic fields produced a 57 percent decrease in mean pain scores at 1 hour ($p < 0.01$) and a 300 percent decrease at 5 hours ($p < 0.001$), persisting to 48 hours postoperatively in the active versus the control group,

along with a concomitant 2.2-fold reduction in narcotic use in active patients ($p = 0.002$). Mean IL-1 beta concentration in the wound exudates of treated patients was 275 percent lower ($p < 0.001$). There were no significant differences found for tumor necrosis factor-alpha, vascular endothelial growth factor, or fibroblast growth factor-2 concentrations. Pulsed electromagnetic field therapy significantly reduced postoperative pain and narcotic use in the immediate postoperative period. The reduction of IL-1 beta in the wound exudate supports a mechanism that may involve manipulation of the dynamics of endogenous IL-1 beta in the wound bed by means of a pulsed electromagnetic field effect on nitric oxide signaling, which could impact the speed and quality of wound repair.

Ian M Rawe, Tracey C Vlahovic. The use of a portable, wearable form of pulsed radio frequency electromagnetic energy device for the healing of recalcitrant ulcers: a case report. Int Wound J 2011. In press

Pulsed radio frequency energy (PRFE) has successfully been used to treat diabetic and venous stasis ulcers. In this case report, a lightweight wearable form of a PRFE device was evaluated and used to treat three diabetic foot ulcers and one venous stasis ulcer. The ulcers were present on the four patients for more than 3 months and had failed to heal after conventional treatment. A lightweight battery-powered, wearable form of PRFE device was introduced as a treatment and used 6–8 hours per day for a period of 6 weeks. All patients after 1 week of therapy showed improvement and wound size was seen to decrease. Patient 1 had a venous stasis ulcer, and reported significant pain relief after 2 weeks treatment. Patients 2 and 3 achieved complete healing after 3 weeks treatment, and patients 1 and 4 had a 95% and 88% reduction in wound size, respectively, after the 6-week study period. Both these patients continued to complete healing using the PRFE device after the 6-week study period. PRFE treatment delivered in the form of a wearable lightweight patch appears to offer promise in the treatment of recalcitrant chronic wounds.

I. M. Rawe, , A.Lowenstein,. C. Raul Barcelo, D. G Genecov. Control of postoperative pain with a wearable continuously operating pulsed radio frequency energy device – a preliminary study. Aesthetic Plast Surg. (2012) 36:458–463

Pulsed radio frequency energy (PRFE) has long been reported to have a therapeutic effect on postoperative pain. In this study, a portable, wearable, low energy emitting form of PRFE therapy device was used to determine the control of postoperative pain following breast augmentation surgery. Eighteen healthy women who underwent breast augmentation entered the study, the procedure performed purely for aesthetic considerations. Postoperative pain following surgery was assessed with a 0-10pt visual analogue scale (VAS). Baseline pain scores were taken on completion of the operation and patients were randomly assigned coded PRFE devices, which were either Active devices or Placebo devices. VAS scores were recorded twice daily for seven days (am and pm). Medication use was also logged for 7 days. The PRFE devices were left in place and in continual operation for the 7 days of the study. All patients tolerated the PRFE therapy well and there were no reported side-effects. VAS scores for the Active group were significantly lower on postoperative day 1. By day 7 the percent of the

baseline VAS remaining in the Active group was 7.9%, compared to the Placebo group of 38%. Along with lower VAS scores, narcotic pain medication use was lower in the patient group who received PRFE therapy. Postoperative pain is significantly lower with PRFE therapy. PRFE therapy in this form is an excellent, drug free and safe method of postoperative pain control.

The Future

These studies have demonstrated that extended wear PRFE have therapeutic benefit that is equivalent to the larger power, short treatment time devices. With continued innovation the concept of extended use wearable PRFE devices can now be fully realized. Overcoming many obstacles Bioelectronics Corporation now offers very small PRFE devices that can worn comfortably for extended periods. They are used for musculoskeletal pain, postoperative pain, and menstrual pain and promote healing of chronic wounds. A series of clinical studies have been carried out demonstrating both safety and efficacy and these studies are present in the following section.

ActiPatch Survey Results



More than a quarter of Americans suffer daily pain, a condition that costs the U.S. about \$60 billion a year in lost productivity.

Introduction

BioElectronics initiated an anonymous survey of customers who had bought and used the ActiPatch product for pain. The survey included questions on the condition that the ActiPatch therapy was used for, how much pain customers were experiencing prior to and post ActiPatch treatment, measured using a 10 point **Visual Analogue Scale (VAS)**. Measuring pain levels with a 10 point VAS, 0 being no pain and 10 being the worst pain, is an accepted method for measuring and assessing pain. A global assessment of the benefits of ActiPatch use, and the effect it had on quality of life, was determined through a standard and widely accepted **Patient Global Impressions of Change (PGIC)** scale. Also assessed was to what extent the use of ActiPatch therapy had on their pain medication consumption. Other general questions asked were, would they purchase another ActiPatch and would they recommend ActiPatch to a friend. A list of the complete survey questions is shown below.

Method

The survey was created by Qualtrics web based survey software (Qualtrics, Provo, UT), and was included as a link in an email to customers who had previously ordered the ActiPatch product. The link took responders to the survey site where the questions were laid out with clear response fields. After completing the anonymous survey the data was submitted by clicking the final 'done' button. Data was compiled over 7 days and totaled 247 responses.

The survey questions were as follows:

- 1. Please write below the main reason for why you used the ActiPatch (eg., back pain, wrist pain, etc)*
- 2. We would like you to describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS and OVERALL QUALITY OF LIFE related to your reason for using ActiPatch.*

*The responses for this question are for the **Patient Global Impressions of Change (PGIC)** scale*

<i>No change or it got worse</i>	☐	1
<i>Almost the same, hardly any change at all</i>	☐	2
<i>A little better, but no noticeable change</i>	☐	3
<i>Somewhat, better, but the change has not made any real difference</i>	☐	4
<i>Moderately better, a slight but noticeable change</i>	☐	5
<i>Better, and definite improvement that has made a real and worthwhile difference</i>	☐	6
<i>A great deal better, and a considerable improvement that has made all the difference</i>	☐	7

3. Below we would like you to indicate by moving the slider, the pain level you were experiencing BEFORE and AFTER the ActiPatch treatment. A score of 0 means no pain and a score of 10 means the worst pain possible.- (The VAS pain assessment).

4. Did you use any pain medication before trying ActiPatch?

5. How did the use of ActiPatch effect on your pain medication use?

<i>Had no effect</i>	1
<i>Reduced the use of pain medication a little</i>	2
<i>Reduced the use of pain medication a moderate amount</i>	3
<i>Reduced the use of pain medication a large amount</i>	4
<i>Eliminated the need for using pain medication</i>	5

6. Where did you first hear about ActiPatch?

7. Where did you purchase ActiPatch?

8. Would you purchase another ActiPatch if the need arises?

9. Would you recommend ActiPatch to a friend?

10. How many hours per day do you use the ActiPatch.

11. How many total days have you used the ActiPatch.

12. Why not? Check all that are applicable.

13. We are interested in how you might respond if a friend asked you to describe the ActiPatch and how it works. Below, briefly write out what you might say telling your friend about how the product works.

14. Is there anything else that you would like to tell us about the product? If so, use the space below.

Results

Question 1. Please write below the main reason for why you used the ActiPatch (eg., back pain, wrist pain, etc)

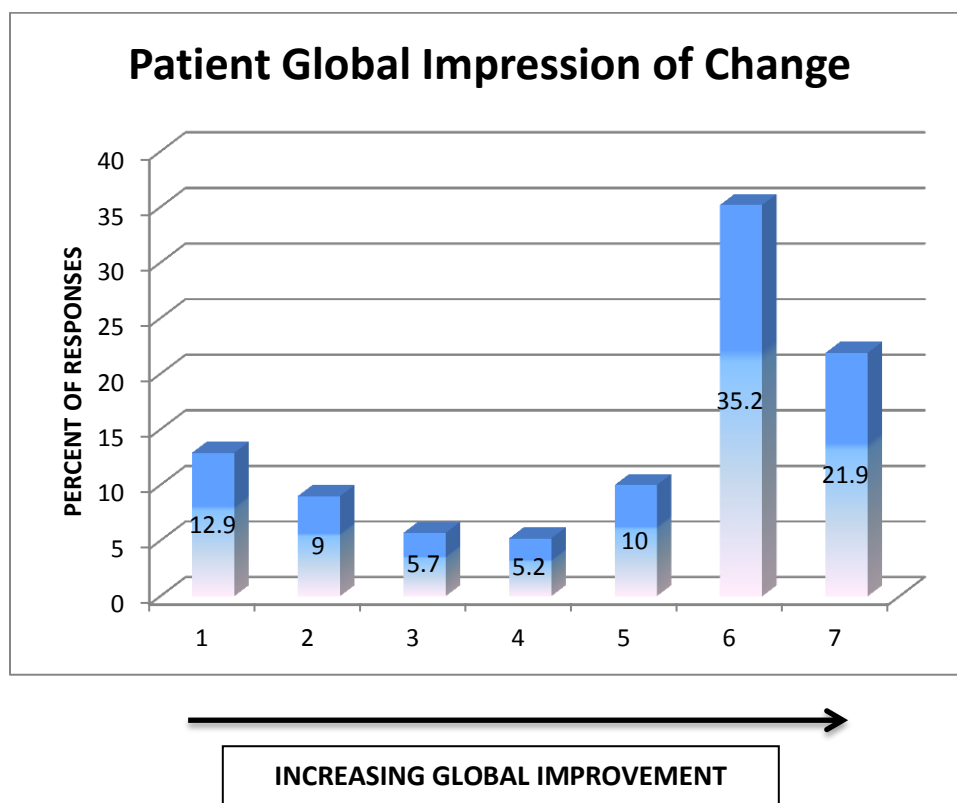
The list of conditions that ActiPatch was used to treat by responders in the survey were as follows:

Back pain (upper and lower) - Knee pain - Shoulder pain - Neck pain - Foot pain - Ankle pain - Toe pain - Wrist pain - Hand pain - Finger/thumb pain - Muscle pain - Leg pain – Fibromyalgia – Tendinitis - Menstrual pain - Multiple uses

Question 2. We would like you to describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS and OVERALL QUALITY OF LIFE related to your reason for using ActiPatch.

The results from the PGIC scale show that ActiPatch use had a significant effect on the improvement in global status rated by responders (figure 1.). 67.1% of survey responders reported a 5, 6 or 7 (moderate to considerable improvement) on the PGIC scale indicating that the ActiPatch has a marked improvement on their overall quality of life.

Figure 1. Patient global impression of change (PGIC) scores expressed as a percent of all survey responders.



1. no change, 2. hardly any change, 3. a little better, 4. somewhat better, 5. moderately better, 6. definite worthwhile improvement, 7. considerable improvement.

Question 3. Below we would like you to indicate by moving the slider, the pain level you were experiencing BEFORE and AFTER the ActiPatch treatment. A score of **0 means no pain and a score of 10 means the worst pain possible.** – (the **visual analogue scale (VAS)** for pain)

The results of the VAS pain question 3 are shown in table 2 and figure 2. Prior to beginning ActiPatch therapy survey responders had a mean reported pain of **7.34** VAS points. This reported pain had declined to 3.54 VAS points after ActiPatch use, a reported drop of **3.8** VAS points. This equates to a 51% decrease in the mean VAS pain. As can be seen from figure 3A there is a meaningful increased decline in VAS pain the longer the ActiPatch was used in hours per day (days of use was between 1 and 22+). Comparing ActiPatch use of less than 3 hours per day to more than 16 hours per day there was a 1.18 VAS points or 40% greater decline in VAS pain in the 16 hour use group. As can be seen from figure 3B the average initial VAS pain was similar between the grouped time data. These results suggest that 16 hrs of use or longer results in the most pronounced pain reduction.

Table 2. Minimum and maximum VAS pain values, as well as Mean VAS pain, and SD.

#	Answer	Min Value	Max Value	Average Value	Standard Deviation	Responses
1	Pain level BEFORE treatment	3.00	10.00	7.34	1.60	238
2	Pain level AFTER treatment	0.00	10.00	3.54	2.70	238

Figure 2. Survey reported VAS pain before and after ActiPatch use.

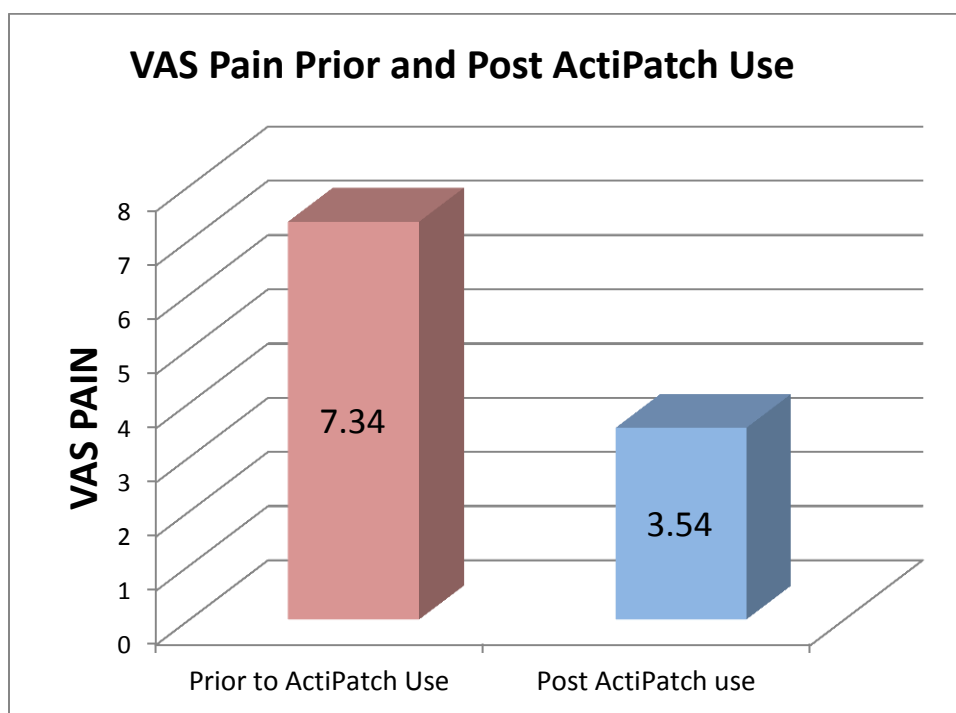


Figure 3A VAS pain decreased in relation to daily hours of ActiPatch use

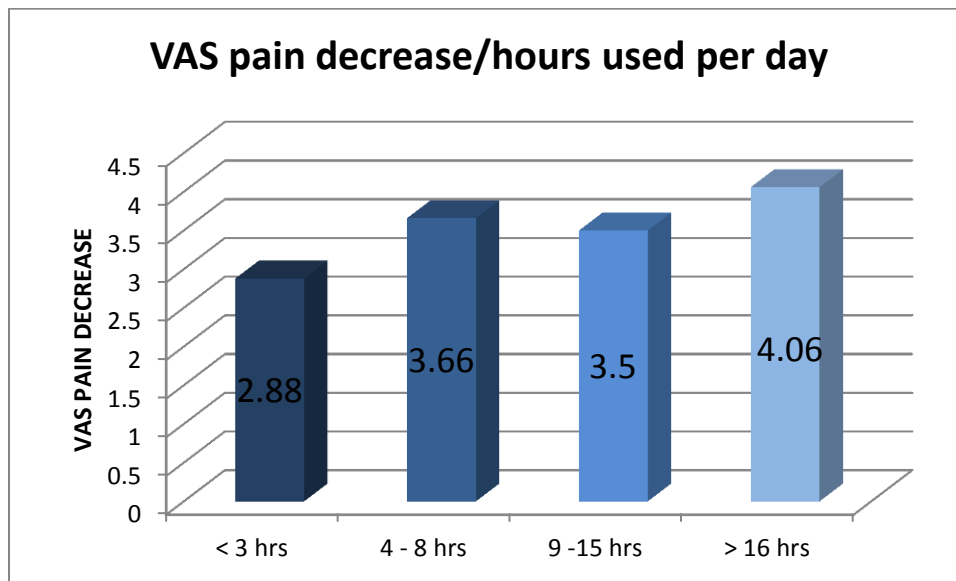
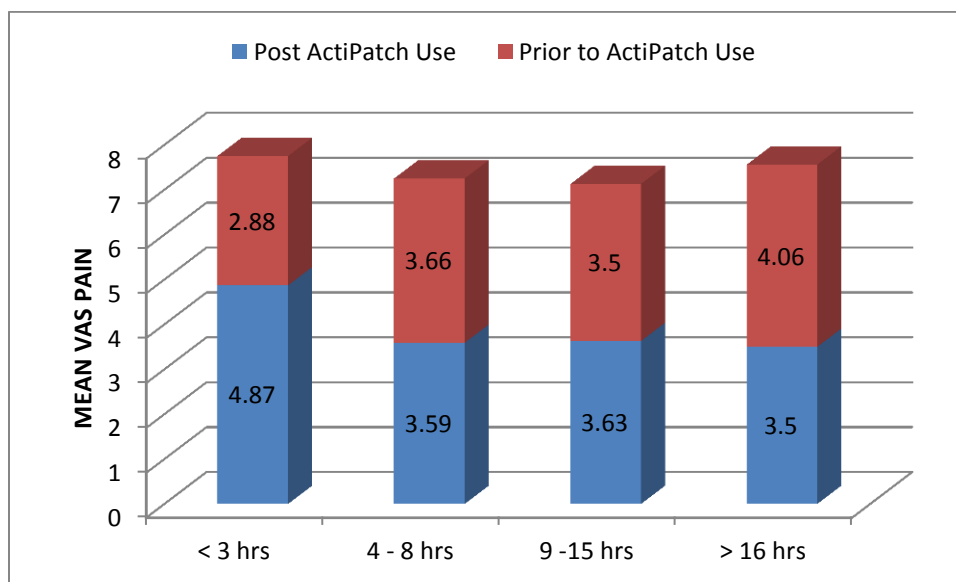


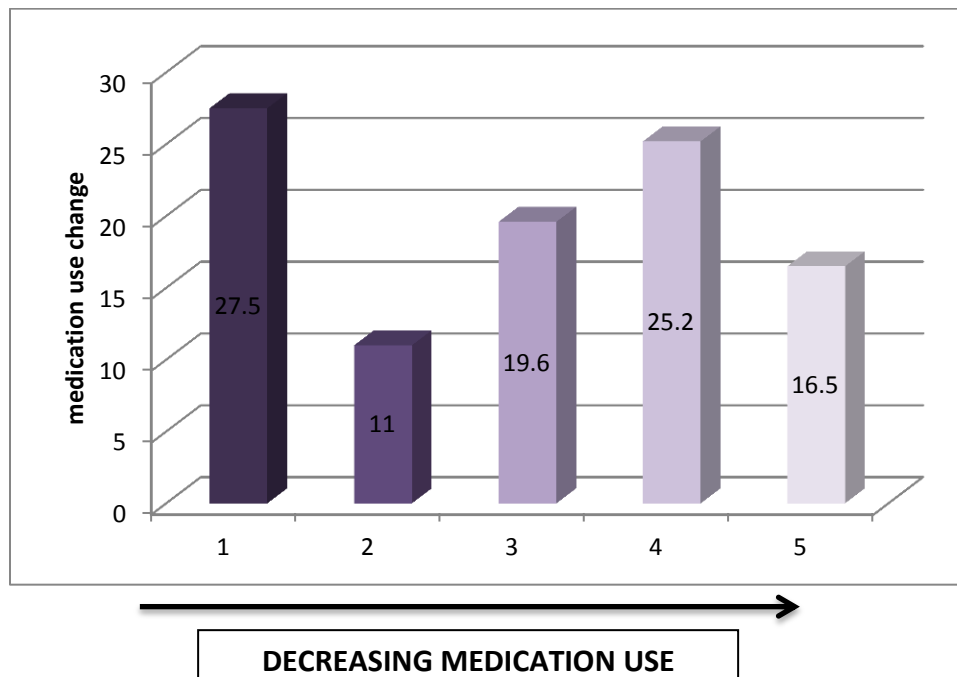
Figure 3B. VAS pain decrease in red and remaining pain (blue) in relation to daily hours used.



Question 4 and 5. Did you use any pain medication before trying ActiPatch? How did the use of ActiPatch effect on your pain medication use?

Of the survey responders 70% indicated that they used pain medications. Figure 4 shows that of these survey responders, 72% reported a reduction in pain medication use, with 61.3% reporting a moderately or greater reduction.

Figure 4. Reduction in pain medication use



Medication use 1. no effect, 2.reduced a little, 3. moderate amount, 4. large amount, 5. eliminated.

Conclusion

The results from the survey indicate that the majority of ActiPatch users benefited from ActiPatch use, experiencing on average a 51% decrease in their pain, a global quality of life improvement and a decreased reliance on pain medications. Taking these three assessment tools together, it can be concluded that ActiPatch is an effective pain therapy for an array of musculoskeletal pain conditions.

Condition Specific VAS pain and PGIC Analysis: Back Pain

Back Pain: The survey responders who used the ActiPatch for back pain (68) were analyzed separately for VAS pain and PGIC scale. The mean average VAS pain score for responders was 7.04 before treatment and 3.51 post ActiPatch treatment and overall decrease in 3.53 VAS points or 50%. PGIC scale scores also showed a global improvement in the majority of responders with 63.7% recording a 5 or greater on the scale.

Conclusion: ActiPatch is an effective therapy for back pain.

Figure 4. VAS pain scores recorded for back pain before and after ActiPatch use

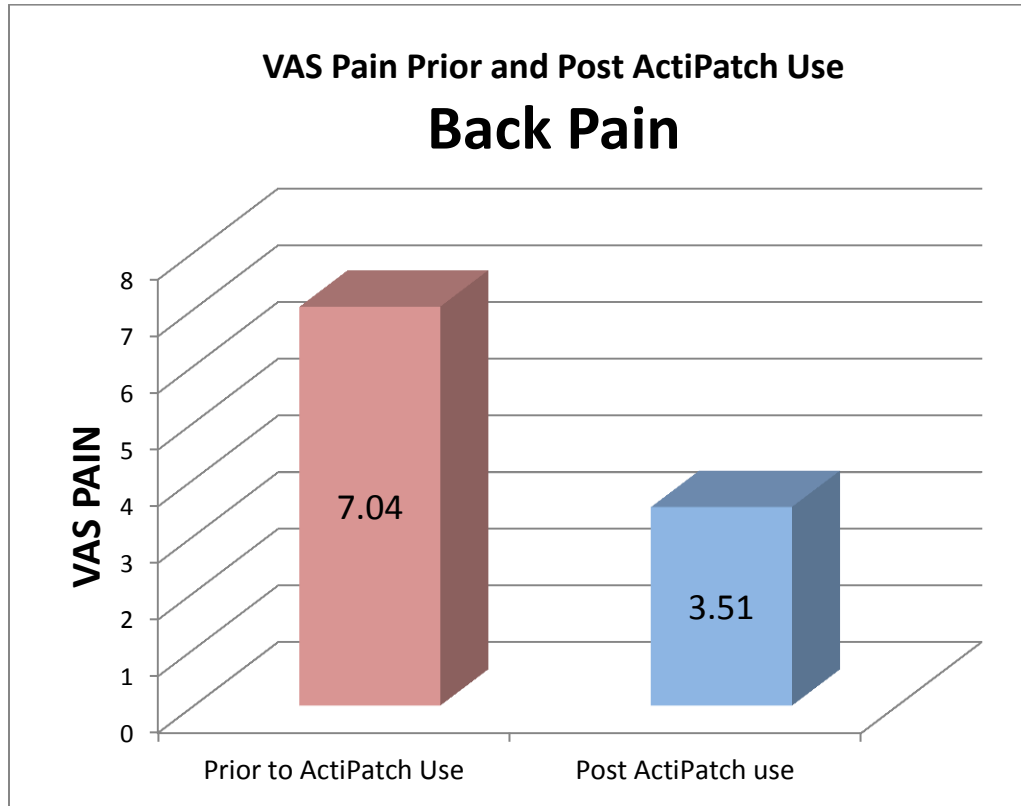
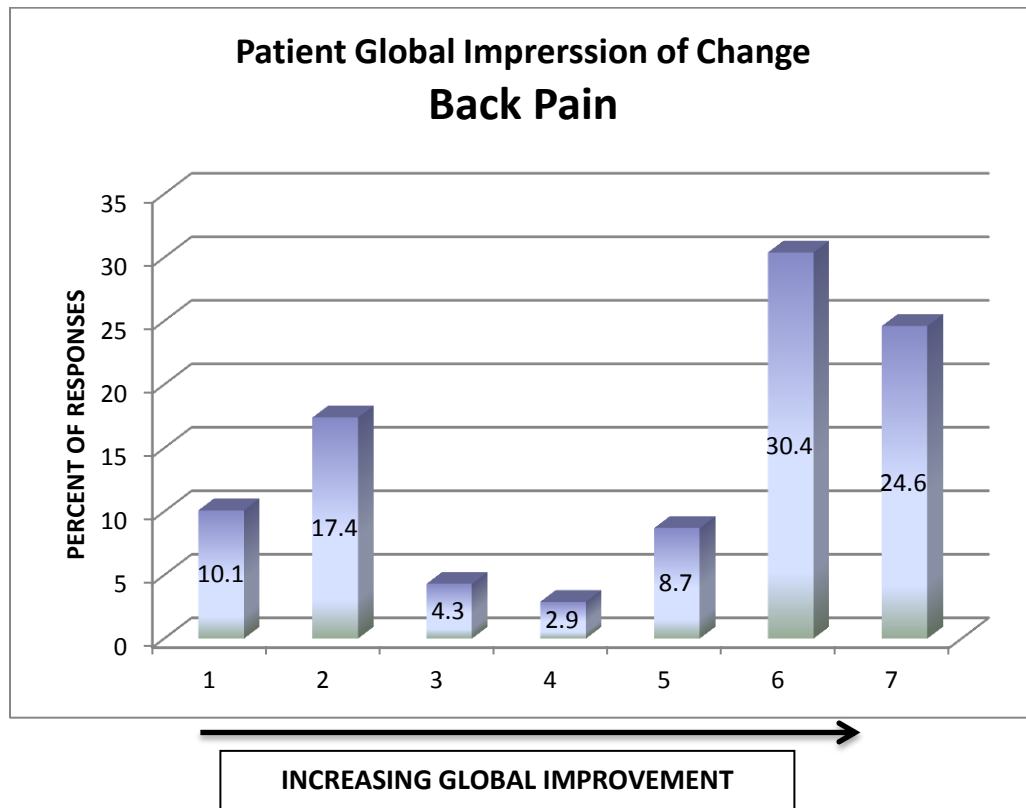


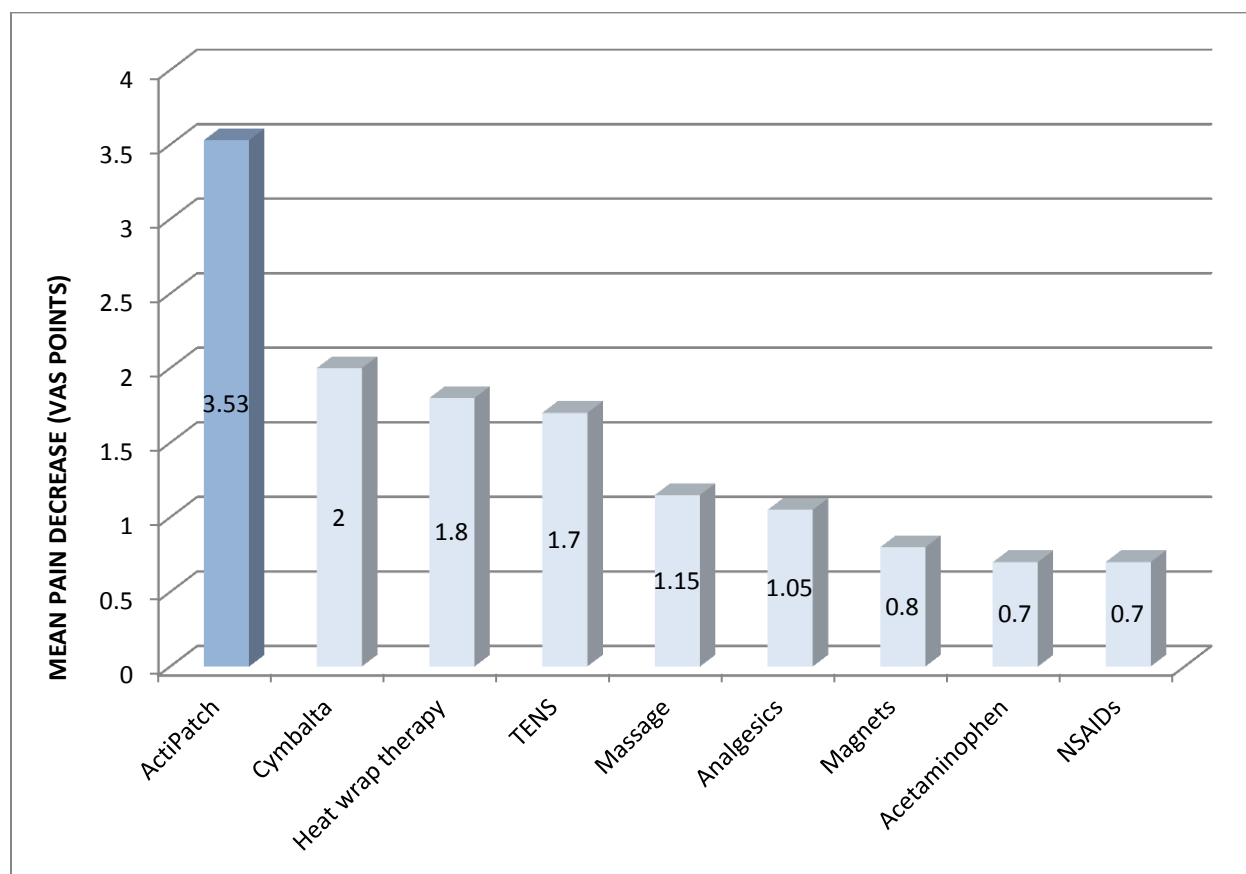
Figure 5. PGIC assessment after ActiPatch use.



ActiPatch - Comparison to therapies for undefined lower back Pain

Data was taken from the following review article - *Analgesic effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials*. L. A. C. Machado, S. J. Kamper, R. D. Herbert, C. G. Maher and J. H. McAuley. *Rheumatology* 2009;48:520–527 – which reported the VAS point decline, the measure of pain reduction, from published randomized controlled trials, or in some cases averaged data from a number of randomized controlled trials, from a diverse number of therapies. The data obtained from the ActiPatch survey from responders reporting the use of ActiPatch for back pain was used to compare to the published data. The decline in VAS pain from ActiPatch use was 3.53 VAS pain points which compares favorably to all the therapies documented in the review article.

Figure 6. A comparison between ActiPatch and published randomized control trial data on a number of therapies shows ActiPatch has the potential to be the therapy with the highest efficacy for back pain.



ActiPatch Compared to Over the Counter Pain Medication – Ibuprofen & Acetaminophen (Paracetamol) on Back Pain

The July 1998 issue of *The American Journal of Medicine* stated the following:

"Conservative calculations estimate that approximately 107,000 patients are hospitalized annually for nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone. The figures of all NSAID users would be overwhelming, yet the scope of this problem is generally under-appreciated."

(June 1999) in the prestigious *New England Journal of Medicine*:

"It has been estimated conservatively that 16,500 NSAID-related deaths occur among patients with rheumatoid arthritis or osteoarthritis every year in the United States. This figure is similar to the number of deaths from the acquired immunodeficiency syndrome and considerably greater than the number of deaths from multiple myeloma, asthma, cervical cancer, or Hodgkin's disease. If deaths from gastrointestinal toxic effects from NSAIDs were tabulated separately in the National Vital Statistics reports, these effects would constitute the 15th most common cause of death in the United States. Yet these toxic effects remain mainly a "silent epidemic," with many physicians and most patients unaware of the magnitude of the problem. Furthermore the mortality statistics do not include deaths ascribed to the use of over-the-counter NSAIDs."

Annual cost of GI hospitalization due to NSAID use is estimated at 2 Billion dollars

Paracetamol hepatotoxicity is, by far, the most common cause of acute liver failure in both the United States and the United Kingdom

Paracetamol overdose results in more calls to poison control centers in the US than overdose of any other pharmacological substance.

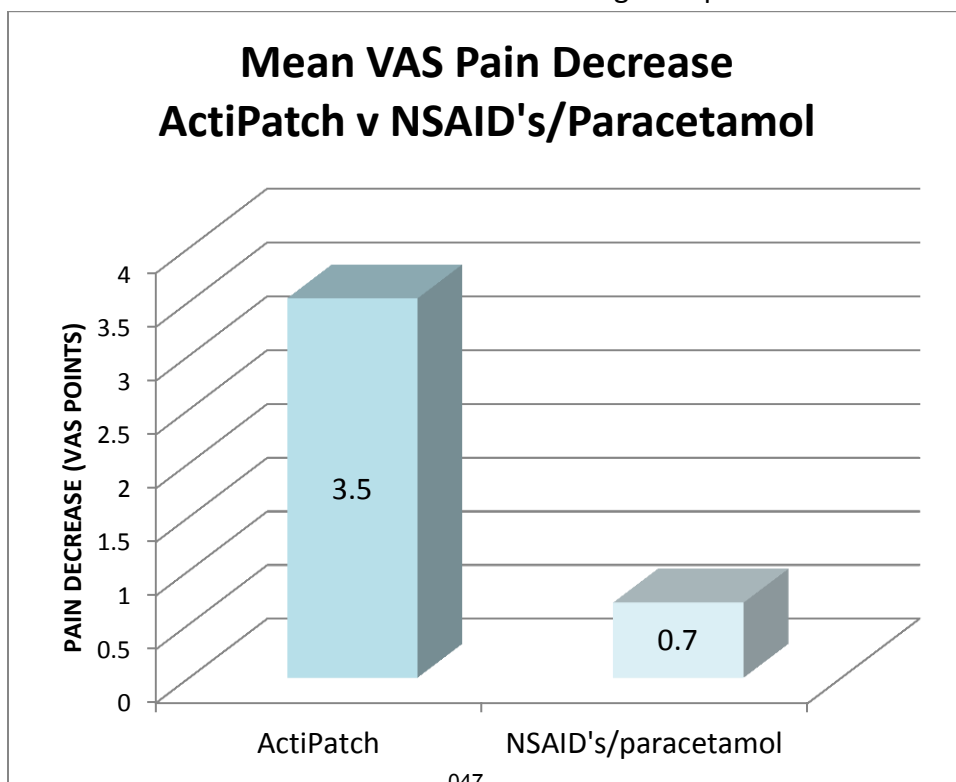
In June 2009, a U.S. Food and Drug Administration (FDA) advisory committee recommended that new restrictions should be placed on paracetamol usage in the United States to help protect people from the potential toxic effects.

The FDA also is requiring manufacturers to update labels of all prescription combination paracetamol products to warn of the potential risk for severe liver injury.

Guidelines for the management of low-back pain in primary care have been published in various countries around the world. All these guidelines recommend the prescription of NSAIDs as one option for symptomatic relief in the management of low-back pain. In most guidelines, NSAIDs are recommended as a treatment option after paracetamol has been tried. Clinical study comparing the two medications indicates that ibuprofen and paracetamol are comparable as an analgesic for back pain.

There have been many published studies documenting the effectiveness of non-steroidal anti-inflammatory drugs (NSAID's) and paracetamol on back pain. NSAID's drugs are often the first choice for people experiencing back pain, however clinical study has shown them to be minimally effective, and have only short-term effects. This is also true for paracetamol. Use of NSAID's also come with a relatively high risk of side effects, commonly with NSAID's these are gastrointestinal related, as NSAID's have an impact on the lining of the stomach. As documented in this peer reviewed paper - *Analgesic effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials*. L. A. C. Machado, S. J. Kamper, R. D. Herbert, C. G. Maher and J. H. McAuley. *Rheumatology* 2009;48:520–527 – NSAID's and paracetamol have a minimal effect on back pain with an average VAS point reduction on back pain of 7mm on a 0 -100mm, or 0.7 points on a 0-10 scale. As shown from our survey results ActiPatch mean VAS point reduction was 3.53 points compared to the reported mean 0.7 point reduction with NSAID's (Figure 7). This comparison indicates that ActiPatch achieves a 5 fold greater pain reduction than commonly used over the counter pain medications - ibuprofen (Motrin, Advil,etc) and paracetamol (Tylenol). ActiPatch has no side effects.

Figure 7. A direct comparison between ActiPatch and NSAID's and paracetamol on the effectiveness of reducing back pain.



Condition Specific VAS pain and PGIC Analysis: Knee Pain

Knee Pain: The survey responders who used the ActiPatch for back pain (83) were analyzed separately for VAS pain and PGIC scale. The mean average VAS pain score for responders was 7.5 before treatment and 3.4 post ActiPatch treatment (figure 8) and overall decrease in 4.1 VAS points or 55%. PIGC scale scores also showed a global improvement in the majority of responders with 72.2% recording a 5 or greater on the scale (figure 9).

Conclusion: Actipatch is an effective therapy for knee pain.

Figure 8. Reported VAS pain before and after ActiPatch use

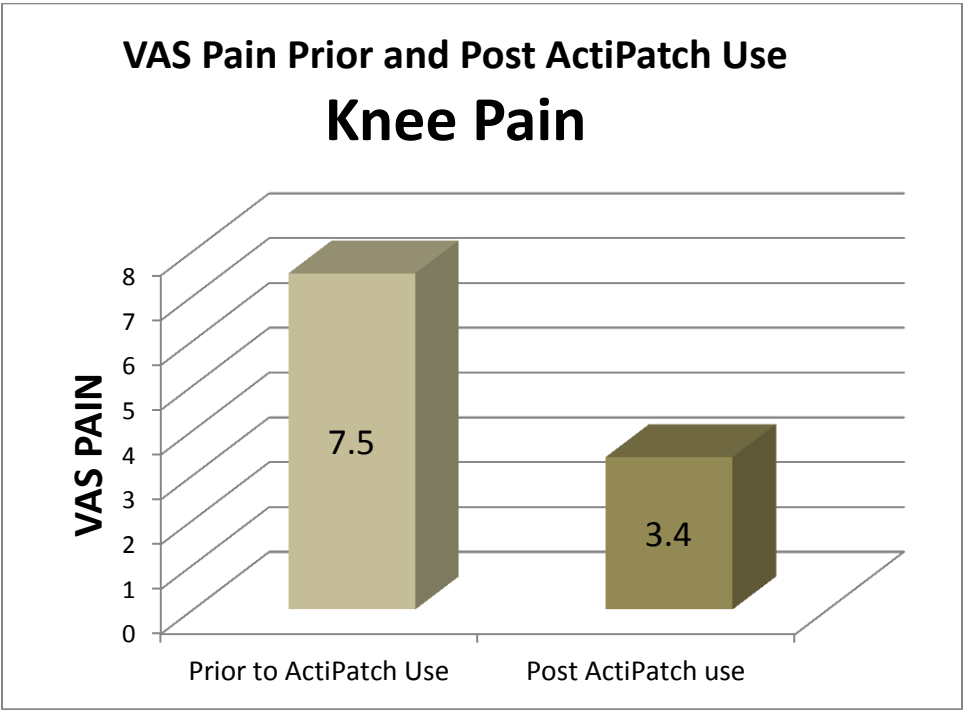
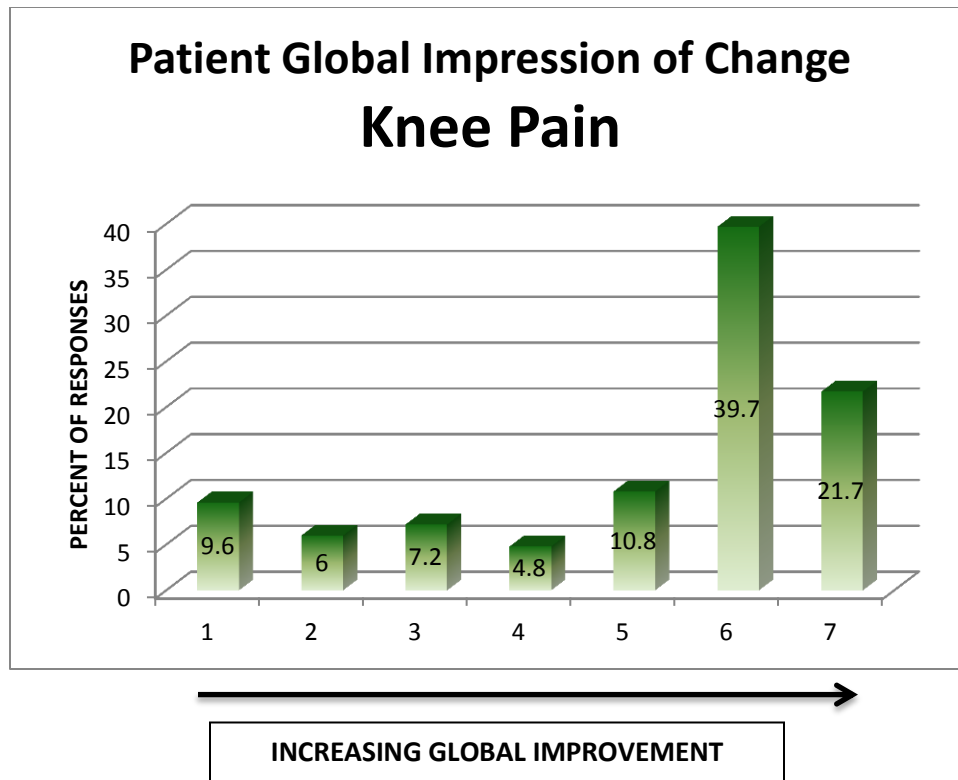


Figure 9. PGIC shows a marked improvement in survey responder quality of life.



ActiPatch Survey Q 8 & 9

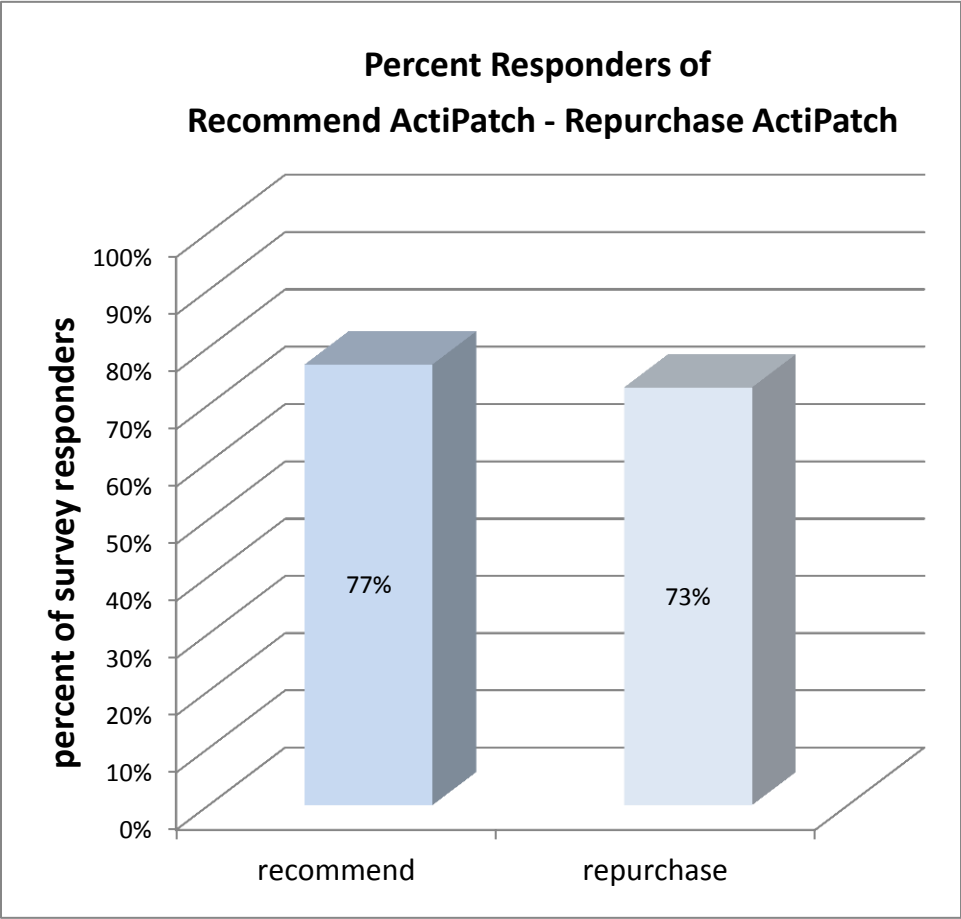
Results of Question 8 and 9:

8. *Would you purchase another ActiPatch if the need arises?*

9. *Would you recommend ActiPatch to a friend?*

Of the survey responders 77% said they would recommend to a friend and 73% responded that they would repurchase another ActiPatch if the need arose.

Figure 9. The survey responders were 77% would recommend ActiPatch and 73% would repurchase.



Use of Radio-Frequency Pulsed Energy in the Control of Postoperative Reaction in Blepharoplasty

Frederick V. Nicolle, M. Chir., F.R.C.S. and Richard M. Bentall, F.R.C.S.

London, England

Abstract. This is a preliminary report of the use of a device to apply small pulses of radio-frequency energy to surgical wounds in order to improve wound healing. The device was applied to one eye in 21 patients who underwent bilateral blepharoplasty. There were no device-related complications. In 11 patients, edema and ecchymosis were noticeably less on the treated side within 24 hours of surgery. In 6 patients, ecchymosis and swelling were so slight that no difference between treated and untreated sides was visible. Two patients were noticeably worse on the treated side. Further studies will be conducted.

Key words: Blepharoplasty — Wound healing — Instrumentation

The first mention in the literature of the use of electricity for healing purposes was possibly Adams in 1799. He recalls the work of Dr. Adam Birch of St. Thomas's Hospital, London, in the 1780's using a Faradic stimulation to assist in the relief of pain and inflammation in a variety of skin conditions [1]. D'Arsonval, a French physiologist in the 1880's, first suggested that a biological system would interact at a molecular and ionic level with electromagnetic fields of various frequencies and encouraged the use of shortwave diathermy for physiotherapy [4]. In more recent times, Ginsberg [7] and Fenn [5] have demonstrated that a pulsed 27.12 megahertz device can aid in the resolution of soft tissue swelling and bruising. In the 1970's, both Wilson [9] and Bentall [3] confirmed that these observations were reproducible in clinical practice. Other means have also been developed of electrically stimulating bone repair in non-unions. Bassett [2], Fukada [6], and Watson [8] used differing devices, all of which in their final interaction with the tissues induce a

current in the tissues secondary to the electric and magnetic field. These devices are large and expensive.

In the past 5 years, a small portable device has been developed by Bentall which has been used in studies on secondary wound healing and on rat abdominal wall tensile strength measurements. These controlled studies, using a placebo device as a control, demonstrated that there was enhancement in the acute wound healing process of 20–30% in these models. The human wound healing study using histological criteria pointed also to a more proficient wound healing process with less pleomorphism in the basal cell layer; almost normal palisading of the basal cells, which is not normally seen in wounds healing from secondary intention; and an almost normal height of re-epithelization compared with the thinned epithelium in the placebo group. These findings encouraged the present study to be undertaken to ascertain the possible clinical role of such a device.

The study reported here was designed to assess the possible benefit of such treatment to patients undergoing cosmetic surgery of the face. Blepharoplasty provided an excellent model, since the lids on each side can be compared for differences in the amount of ecchymosis and edema.

Material and Methods

The device itself consists of a small oscillator tuned to 27.12 megahertz with a timer switching the oscillator so that small pulses of radio-frequency energy are emitted from the single turn coaxial coil. The shape of the pulse is square and is 100 μ sec long, there being 1,000 pulses per second. The power is from a small nickel-cadmium rechargeable 3.5-volt DC battery which draws 0.5 ma; the unit may be used for 5 days without recourse to recharging. The area of the coil is approximately 6 cm in diameter.

Address reprint requests to Frederick V. Nicolle, 30 Harley Street, London W1N 1AB, England



Fig. 1. A patient who underwent upper and lower blepharoplasty on both right and left eyes. The right eye was treated with Bentall's device and illustrates the typical response noted in 11 out of 13 cases where sufficient ecchymosis and edema existed for comparison. In this case, although ecchymosis is similar in both eyelids, the degree of edema is obviously greater in the untreated left eye. This difference is most obvious 24 hours postoperatively, but the relative improvement is apparent throughout the period of observation. (A) One day postoperatively. (B) Three days postoperatively. (C) Six days postoperatively.

In order to adapt this device to fit over the eyelid region, 2 wire loops were designed in the shape of a spectacle frame which can then be held in place with light padding and a 2-in crepe bandage. Only 1 loop is electrically active, the other providing a control. This device was applied at completion of surgery and removed after 24 hours. The device showed no indication as to which side was active, and this was only known to the manufacturer.

For the purpose of the preliminary report, 21 consecutive cases of blepharoplasty were treated. Photographs were taken 24 hours postoperatively when the bandage was removed, after 3 days when the sutures were removed, and after 6 days follow-up. Some cases were of upper and lower blepharoplasty, others of one set of lids only (Fig. 1). Some were operated on under local anesthetic and others under general. No attempt was made to subdivide this group, since a study of all the patients in a

consecutive series was considered to be the most valid basis for comparison.

Results

Twenty-one patients were studied, and the postoperative course of all of them was uncomplicated by any contributory factors such as vomiting, coughing bouts, or trauma which might have influenced the result. Two cases were excluded because of displacement of the dressings by the patients. No patient complained of any unusual pain locally or headaches that might have been interpreted as related to the electrical treatment.

In 6 cases, ecchymosis and swelling was so slight that no difference was visible between the treated and untreated sides. In 11 cases, improvement was apparent, which was most obvious at 24 hours when treatment was ended. At this point edema, and to a lesser extent ecchymosis, was distinctly less on the treated side, and this improvement continued to be apparent after 6 days when the period of early follow-up ended. Two cases were judged to be worse on the treated side.

Discussion

A patient's most immediate concern following facial cosmetic surgery is whether they will experience much bruising, swelling, or pain, and how long this will take to recover to a point when it will pass unnoticed during social contact. This series is small, but the results are so encouraging that reporting it seems justified. Of course, the study will continue and a much larger number of cases will be added to this study in the immediate future.

We are also now employing a similar device for incorporation in face and neck lifts, which is identical electrically but has two larger wire loops to cover the neck and sides of the face. Devices such as Bentall's have immense possible benefits to plastic surgery cases, not only in cosmetic cases but in so many situations where the rate of healing and reduction of edema and ecchymosis are of considerable importance. We look forward to reporting later on a much expanded series.

References

1. Adams G: An Essay on Electricity, Explaining the Principles of That Useful Science, and Describing the Instruments. 5th Edition, Dillon and Co., 1799, pp 482-575
2. Bassett CAL, Pawluk RJ, Pills AA: Augmentation of

- bone repair by inductively coupled electromagnetic fields. *Science* **184**:575, 1974
3. Bental RHC, Eckstein HB: A trial involving the use of pulsed electromagnetic therapy on children undergoing orchidopexy. *Kinderchirurgie* **17** (no. 4) November, 1975
 4. D'Arsonval A: New method of electrical stimulation/exultation of nerves and muscles. *CR Acad Sci (Paris)* **92**:1520, 1881
 5. Fenn JE: Effect of pulsed electromagnetic energy (Diapulse) on experimental haematomas. *Canad Med Assoc J* **100**:251, 1969
 6. Fukada E, Takamatsu T, Yasada I: Callus formation by electret. *Jpn J Appl Phys* **14**:2079, 1975
 7. Ginsberg AJ: A description of my athermic short wave apparatus with clinical applications. *NY Acad Med* October 14, 1940
 8. Watson J, Downes EM: The application of pulsed magnetic fields to the stimulation of bone healing in healing. *Jpn J Appl Phys* **17**:215, 1978
 9. Wilson DH: Treatment of soft tissue injuries by pulsed electrical energy. *Br Med J* **2**:269, 1972

Control of Postoperative Pain with a Wearable Continuously Operating Pulsed Radiofrequency Energy Device: A Preliminary Study

Ian M. Rawe · Adam Lowenstein · C. Raul Barcelo · David G. Genecov

Received: 18 May 2011 / Accepted: 29 September 2011 / Published online: 25 October 2011
© Springer Science+Business Media, LLC and International Society of Aesthetic Plastic Surgery 2011

Abstract

Background Pulsed radiofrequency energy (PRFE) has long been reported to have a therapeutic effect on postoperative pain. In this study, a portable, wearable, low-energy-emitting PRFE therapy device was used to determine the control of postoperative pain after breast augmentation surgery.

Methods The study enrolled 18 healthy women who underwent breast augmentation purely for aesthetic considerations. Postoperative pain after surgery was assessed with a 0- to 10-point visual analog scale (VAS). Baseline pain scores were taken at completion of the operation, and the patients were randomly assigned coded PRFE devices that were either active or placebo devices. For 7 days, VAS scores were recorded twice daily (a.m. and p.m.). Medication use also was logged for 7 days. The PRFE devices were left in place and in continuous operation for the 7 days of the study.

Results All the patients tolerated the PRFE therapy well, and no side effects were reported. The VAS scores for the active group were significantly lower on postoperative day 1. By day 7, the baseline VAS remaining in the active group was 7.9% versus 38% in the placebo group. Together with lower VAS scores, narcotic pain medication use was lower in the patient group that received PRFE therapy.

Conclusion Postoperative pain is significantly lower with PRFE therapy. According to the findings, PRFE therapy in this form is an excellent, safe, drug-free method of postoperative pain control.

Keywords Pain · Postoperative · Pulsed radiofrequency

Postoperative pain after surgery is a major priority for both patients and doctors. Pain affects blood pressure, heart rate, appetite, and general mood. Despite advances in our understanding concerning the neurobiology of nociception, the development of new analgesics, and the refining of minimally invasive surgical techniques, postoperative pain continues to be undertreated [1]. A 2003 survey of pain management in the United States shows that there still is a need to enhance postoperative pain management [2].

Improvement of effective analgesia in the early postoperative period may lead to clinically important benefits in terms of long-term recovery, including a decreased incidence of chronic postsurgical pain [3]. Chronic pain after breast cancer surgical treatment, for example, is a major clinical problem, affecting 25–60% of patients [4]. An added benefit of improved analgesia is enhanced recovery, with shortened hospital stays and convalescence [5, 6].

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 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) [7] for medical use. The frequency of 27.12 MHz is the most widely used in clinical practice.

I. M. Rawe (✉)
BioElectronics Corporation, 4539 Metropolitan Court,
Frederick, MD 21704, USA
e-mail: ian.rawe@gmail.com

A. Lowenstein
Montecito Center for Aesthetic Plastic Surgery,
Santa Barbara, CA, USA

C. R. Barcelo · D. G. Genecov
Genecov Plastic Surgery Group, Dallas, TX, USA

The first PRFE device, the Diapulse (Diapulse Corporation, Great Neck, NY, USA), was commercially available in the 1950s. It was followed by other commercially available machines. As a treatment for nonhealing bone fractures in humans, the use of PEMF is well established [8] and has been in use since the 1970s. Clinical studies have 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 [9, 10]. Studies on postoperative pain also showed good results [11–13]. Reduction of capsular contraction in 41 patients after breast augmentation surgery was achieved with PRFE therapy together with massage and closed capsulotomy treatment [14]. Pain and edema also have been treated with PRFE therapy in a number of orthopedic conditions [7, 15–18].

Findings also have demonstrated PRFE therapy to be effective for chronic wounds, including diabetic and venous stasis ulcers. A number of early studies showed good results [19], with improved healing of pressure ulcers with PRFE treatment [20].

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 for the healing of recalcitrant, predominantly venous leg ulcers. Significant decreases in wound depth and pain intensity favoring the active group were observed [21].

Important recent studies on the 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 Regenesi Biomedical Wound-Healing Registry [24] (Regenesi 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 [26]. The second study, using the same form of wearable PRFE device after breast reduction surgery, also showed significant control of postoperative pain [27]. In this study, a decrease in interleukin 1- β was reported, suggesting a modulation of the wound-healing process.

A potential mechanism of action for PRFE therapy has been put forward and is reviewed by Strauch et al. [28]. Moreover, recent reports have further contributed to understanding concerning the mechanisms of PRFE therapy for wound healing [29, 30].

Continued technological advancement has allowed PRFE devices to be produced that are smaller and less obtrusive, as shown in Fig. 1 (BioElectronics Corp, Frederick, MD,

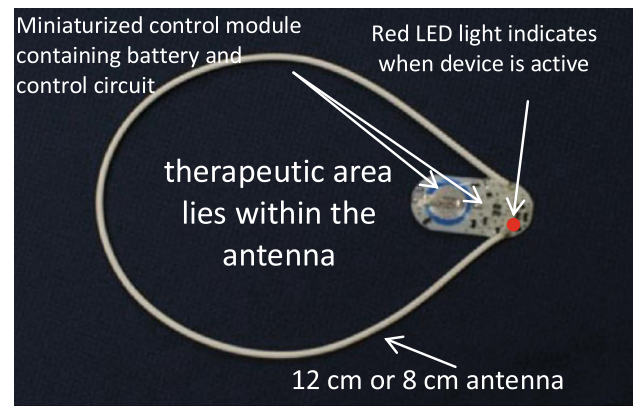


Fig. 1 Latest version of a pulsed radiofrequency energy (PRFE) device. The therapeutic field lies within the 12-cm antenna. The control module containing the battery is small (4.2×2.0 cm, with a depth of 0.3 cm) and streamlined, allowing for comfortable application

USA). The small size allows them to be potentially applied to most areas of the body. They are inexpensive to produce and easy for both the physician and the patient to use.

Materials and Methods

Patients

The ethics review board of North Texas Independent Review Board at Medical City, Dallas, Texas approved this study. All the patients enrolled in the study signed a consent form.

PRFE Device

The device used in this study was a PRFE device (RecoveryRx, BioElectronics Corp) that emits a safe form of non-ionizing electromagnetic radiation. The carrier frequency of this device is 27.12 MHz, the assigned FCC medical frequency. It has a pulse rate of 1,000 pulses per second and a 100- μ s burst width. The peak burst output power of the 12-cm antenna is approximately 0.0098 W covering a surface area of approximate 100 cm². The circuitry consists of low-voltage (3 V) digital/analog electronics that control all timing functions to produce the therapeutic RF field with the antenna field placed directly above the therapeutic site.

Study Design

The study was a double-blind, placebo-controlled randomized study to determine postoperative pain after breast augmentation. The 18 patients recruited into the study had elected the surgery for purely aesthetic reasons. Silicone breast implants (Allergan, Irvine, CA, USA) were used for

all the patients, and each operation was performed in less than 1 h.

Breast augmentation was performed in submuscular fashion via either an inframammary or periareolar approach. Randomization resulted in 10 patients receiving active devices on each breast and 8 patients receiving placebo devices on each breast. There were no patient dropouts. The demographics of the active and placebo patient groups very closely matched in terms of average age (32 vs. 31.3 years), weight (134.4 vs. 134.1 lb), and height (5.61 vs. 5.44 ft).

Once the surgery was completed, the PRFE devices were activated and secured in place with a surgical bra. The placebo devices were activated in the same way. A red indicator light showed activation of both the placebo and active devices. The active devices were not felt by the patient, ensuring that the patients were unable to determine the treatment group.

At completion of the operation, a baseline score was assessed for each patient. The pain scores were assessed using a visual analog scale (VAS) ranging from 0 (no pain) to 10 (extreme pain). The pain scores were logged in the a.m. and p.m. for the 7 days of the study. The use of VAS scores to document pain is well established [31]. The medication use by each patient also was logged. The medications used by patients were opiate-based drugs, oxycodone, hydrocodone, and propoxyphene.

Statistical Analysis

Means with standard deviations are reported. The differences between the active and placebo groups were determined by *t*-tests and repeated measures analyses of variance (ANOVA). The *F*-test for the equality of variances was performed. A *P* value of 0.05 was considered significant.

Results

The PRFE therapy devices were well tolerated by all the patients, and no adverse effects were noted. Data were obtained from all the patients and available for statistical analysis. The baseline score, obtained at completion of the operation before treatment, did not differ significantly between the active and placebo groups. Therefore, the baseline VAS score was determined from all the patients. The VAS scores, collected twice daily (a.m. and p.m.), were averaged to a daily mean. The mean daily VAS scores and standard deviations are presented in Table 1.

The mean baseline VAS score was 6.46 on the 0- to 10-point scale. As shown in Fig. 2, the postoperative day 1 VAS score for the active group was 2.06 points lower than

Table 1 Mean daily visual analog scale (VAS) scores and standard deviations for the active group (A-VAS) and the placebo group (P-VAS) during the 7 days of the study

Day	P-VAS	A-VAS
Baseline	6.46 ± 1.98	6.46 ± 1.98
1	6.80 ± 1.74	4.40 ± 2.09
2	5.20 ± 2.08	3.85 ± 2.36
3	5.40 ± 2.21	2.57 ± 1.32
4	4.25 ± 2.37	2.00 ± 1.27
5	3.40 ± 1.99	1.55 ± 1.23
6	3.80 ± 2.01	0.75 ± 0.65
7	2.40 ± 1.02	0.50 ± 0.40

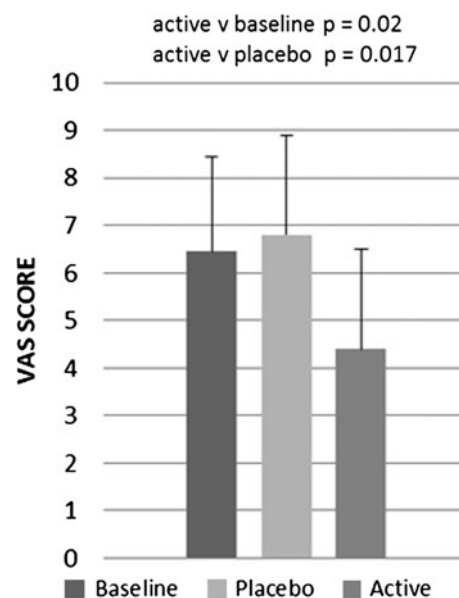


Fig. 2 On postoperative day 1, the active group mean visual analog scale (VAS) score at 4.40 is significantly lower than the mean baseline score of 6.46 ($P = 0.02$) and the placebo mean VAS score of 6.80 ($P = 0.017$)

the baseline score ($P = 0.02$, significant difference). The placebo group VAS score was 6.80, which was not significantly lower than the baseline score ($P = 0.65$). The VAS score for the active group was 2.40 points lower than that for the placebo group ($P = 0.017$, significant difference).

The VAS scores in the active group were significantly lower than the placebo group on all days except day 2 ($P = 0.23$), but were 1.35 VAS points (35%) lower. Figure 3 shows the comparison of the active and placebo VAS scores with the baseline score at postoperative day 3. On postoperative day 3, the placebo group VAS was 5.40 points. The active mean VAS score (2.57) was significantly lower than the placebo mean VAS score (5.40) on day 3 ($P = 0.003$), showing a difference of 2.83 points. The

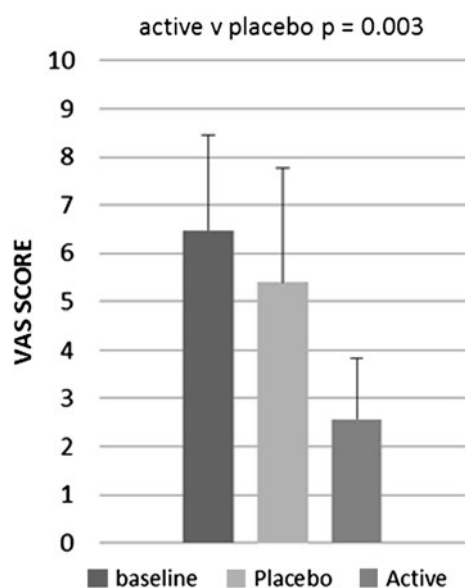


Fig. 3 On postoperative day 3, the mean visual analog scale (VAS) score is 2.83 points lower in the active group than in the placebo group and has recovered 60% from the baseline score compared with a 17% recovery in the placebo group ($P = 0.003$)

active group recovered to 50% of baseline pain between postoperative days 2 and 3, whereas the placebo group recovered to 50% of baseline by postoperative day 6. These results show that the active group recovered faster than the placebo group.

Narcotic Pain Medication

The pain medication was logged by each patient on a daily basis. Patients used narcotic pain medication consisting of oxycodone 2.5/325 (O), hydrocodone 5/500 (H), hydrocodone 7.5/500 (H+), and propoxyphene (P). The total narcotic pain pill use was 145 pills in the placebo group (81 H, 9 H+, 55 O) and 110 pills in the active group (67 H, 2 H+, 26.5 O, 14.5 P). The individual patient use of narcotic pain pills in the active group was as follows: 2.5, 4, 5, 6, 7, 10, 14, 14, 14.5, and 33. In the placebo group, the individual narcotic pill use was 6, 13, 18, 19, 20, 21, 23, and 23. Of the 10 patients in the active group, 6 patients used 10 or fewer narcotic pain pills. One patient in the placebo group used 10 or fewer narcotic pain pills. A single patient in the active group used 33 narcotic pain pills (H). This represents

30% of the total narcotic medication use in the active group and more than twice as much as the next highest total of 14.5.

The statistics for patient use of narcotic medication are shown in Table 2. The means were 11 pills per patient in the active group and 18.1 pills per patient in the placebo group, representing a 68% increase in narcotic medication use in the placebo group ($P = 0.07$, nonsignificant increase). However, with the outlier (patient 10) excluded, the mean narcotic pill use becomes 18.1 for the placebo group and 8.5 for the active group ($P = 0.002$, a significant difference). The median value, which better controls for any outliers in the data set provides a more representative value for pain pills per patient in the active group. The median number of prescription pills per patient was 8.5 in the active group and 20 in the placebo group.

Discussion

The 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 totaling the mean VAS points for each day resulted in an accumulated average total of 31.25 VAS points for the placebo patient group and 15.62 VAS points for the active group during the 7-day study period. This indicates that the active group patients experienced an average of 50% 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 still were experiencing 37% of the baseline VAS score, whereas the active group had 7.7% of the baseline VAS score remaining. Thus, the placebo group continued to experience significant pain beyond day 7. This was highlighted by the fact that the day 7 placebo VAS point mean of 2.40 was equivalent to the day 3 VAS point mean of 2.57 in the active group.

The data presented also show that the patients who received PRFE therapy required less narcotic pain medication, which is not surprising, because with lower pain scores, less pharmacologic pain medication use would be expected. Taken together, decreased postoperative pain and lower narcotic medication use suggests that postsurgical complications would be reduced and that opiate-related

Table 2 Total narcotic pills used by patient group

	Total	Mean	SD	Median	<i>P</i> value	Total	Mean	SD	Median	<i>P</i> value
Placebo	145	18.1	5.9	20	–	145	18.1	5.9	20	–
Active	110	11.0	8.9	8.5	0.07	77	8.5	4.6	7	0.002

Mean, median, SD, and *P* value as well as the total, mean, median, SD, and *P* value with the outlier removed (italics)

SD standard deviation

side effects also would be less frequent. These data therefore indicate that PFRE is a safe and effective method for combating postoperative pain.

The pain medication side effects of opiate-based, acetaminophen, and nonsteroidal antiinflammatory (NSAID) drugs have been well documented. The side effects of opiate drugs are postoperative nausea and vomiting, urinary retention, ileus, constipation, and sedation. With acetaminophen and NSAIDs, side effects such as hepatic and renal toxicity, coagulation, confusion, sedation, and dizziness have been reported.

To improve analgesia and combat these side effects, the concept of multimodal, or balanced analgesia was introduced aimed at combining analgesics with additive or synergistic effects [32]. The theory behind this approach is that varying combinations of drugs for managing postoperative pain improve safety and efficacy due to their different mechanisms of action. There is some indication that this has led to a reduction in opioid-related side effects and improved analgesia [33, 34]. However, patient pain surveys indicate that postoperative pain management still is in need of significant improvement [2, 32]. Delivered in this form, PRFE energy would add another dimension to the multimodal analgesia approach. However, to be widely used and accepted, the PRFE device needs to be unobtrusive and seamlessly applied to wound dressing and recovery protocols. The RecoveryRx device used in this study is a one-time-use disposable device that operates for a minimum of 7 days, requires minimal patient involvement, and is very economical to produce.

Figure 1 shows the latest version of the PRFE device. The control module containing the battery measures 4.2×2.0 cm and has a depth of 0.3 cm. With a 12- or 8-cm antenna, the device weighs 8 g and could be simply applied for most surgical recovery protocols without having an impact on patient comfort while improving outcome. Whereas this study demonstrates the control of postoperative pain, this form of lightweight, wearable PRFE device also has been shown to promote the healing of chronic wounds [25].

The results of the study presented in this report show control of postoperative pain using a unique, continuously operating low-energy PRFE device. The control of postoperative pain is equivalent to that in the breast augmentation study by Heden and Pilla [26], with both studies showing significantly lower VAS scores by postoperative day 3 and both studies using portable wearable PRFE devices. However, the two studies had major differences. The PRFE device used in the Heden study was the Ivivi Technologies Torino, which has a higher peak output at 0.5 W than the RecoveryRx at 9.8 mW. The operation of the Ivivi device follows a protocol of being on initially 30 min every 4 h for the first 3 days, then 30 min every 8 h for the next 3 days. This contrasts with the continuous

operation of the RecoveryRx device used in this study and shows that continuous low-energy application is as effective as a shorter treatment time with higher-energy devices in controlling postoperative pain. The most significant difference is the physical size of the two PRFE devices used in the studies. The Ivivi Technologies Torino has a weight of 28 g, a 15- or 19-cm antenna, and a control module with an approximate size of 6.35×6.22 cm and a depth of 1.68 cm. The weight of the Ivivi device and the size of its control module are therefore about 3.5 times greater.

The concept of replacing short high-power PRFE energy treatments with extended-use, low-energy treatments was first developed by Dr. Bentall, who presented data comparing the effects of a 15-W PRFE device at 27.12 MHz (Diapulse) with those of a 2-mW pulsed device at 3 MHz on the tensile strength of rat abdominal wounds [35]. Despite the large difference in the physical size and power output of the two devices, they showed a very similar profile in enhancing the tensile strength of the wounds. The 15-W Diapulse treatment was given for 20 min three times per day, whereas the 2-mW treatment was an overnight exposure. The control condition was a 15-W light bulb. Applying this concept to postoperative recovery, Nicolle and Bentall [10] demonstrated the control of edema and bruising during postoperative recovery from blepharoplasty using a low-energy, extended-use PRFE device.

Larger-scale clinical trials still are needed for further validation of this postoperative therapy. However, the findings have shown the use of RecoveryRx PRFE therapy in a clinical setting to be as effective as the results presented in this report. For example, RecoveryRx is estimated to reduce postoperative pain by 60% after cesarean section (personal communication with Ian Rawe from Charge Nurse, Labor, and Delivery Ward).

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

Conflict of interest David G. Genecov received honoraria from BioElectronics Corporation for the study. Ian M. Rawe is a paid consultant for BioElectronics Corporation.

References

1. White PF (2008) Pain management after ambulatory surgery: where is the disconnect? *Can J Anaesth* 55:201–207
2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ (2003) Postoperative pain experience: results from a national survey suggest

- postoperative pain continues to be undermanaged (table of contents). *Anesth Analg* 97:534–540
3. Buvaendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ (2010) Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg* 110:199–207
 4. Andersen KG, Kehlet H (2011) Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. *J Pain* 12:725–746
 5. White PF, Eng M (2007) Fast-track anesthetic techniques for ambulatory surgery. *Curr Opin Anaesthesiol* 20:545–557
 6. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, Carli F (2007) The role of the anesthesiologist in fast-track surgery: From multimodal analgesia to perioperative medical care (table of contents). *Anesth Analg* 104:1380–1396
 7. Foley-Nolan D, Barry C, Coughlan RJ, O'Connor P, Roden D (1990) Pulsed high-frequency (27 MHz) electromagnetic therapy for persistent neck pain: a double-blind, placebo-controlled study of 20 patients. *Orthopedics* 13:445–451
 8. Aaron RK, Ciombor DM, Simon BJ (2004) Treatment of non-unions with electric and electromagnetic fields. *Clin Orthop Relat Res* 419:21–29
 9. Aronofsky DH (1971) Reduction of dental postsurgical symptoms using nonthermal pulsed high-peak-power electromagnetic energy. *Oral Surg Oral Med Oral Pathol* 32:688–696
 10. Nicolle FV, Bentall RM (1982) Use of radiofrequency pulsed energy in the control of postoperative reaction in blepharoplasty. *Aesthet Plast Surg* 6:169–171
 11. Benazzo F, Zanon G, Pederzini L, Modonesi F, Cardile C, Falez F, Ciolli L, La Cava F, Giannini S, Buda R et al (2008) Effects of biophysical stimulation in patients undergoing arthroscopic reconstruction of anterior cruciate ligament: prospective, randomized, and double-blind study. *Knee Surg Sports Traumatol Arthrosc* 16:595–601
 12. Till M, Gubisch W, Frickert G, Reichert H, Schmidt KH (1993) Postoperative management with pulsed high-frequency electromagnetic energy: a clinical study of 38 patients with rhinoseptoplasty. *Handchir Mikrochir Plast Chir* 25:26–32
 13. Frank R (1985) Treatment of the perineum by pulsed electromagnetic therapy. *Midwives Chron* 98:297–298
 14. Silver H (1982) Reduction of capsular contracture with two-stage augmentation mammoplasty and pulsed electromagnetic energy (Diapulse therapy). *Plast Reconstr Surg* 69:802–808
 15. Foley-Nolan D, Moore K, Codd M, Barry C, O'Connor P, Coughlan RJ (1992) Low-energy high-frequency pulsed electromagnetic therapy for acute whiplash injuries: a double-blind randomized controlled study. *Scand J Rehabil Med* 24:51–59
 16. Pennington GM, Danley DL, Sumko MH, Bucknell A, Nelson JH (1993) Pulsed, nonthermal, high-frequency electromagnetic energy (Diapulse) in the treatment of grade I and grade II ankle sprains. *Mil Med* 158:101–104
 17. Wilson DH (1974) Comparison of short-wave diathermy and pulsed electromagnetic energy in treatment of soft tissue injuries. *Physiotherapy* 60:309–310
 18. Cameron BM (1964) A three-phase evaluation of pulsed, high-frequency, radio short waves (Diapulse): 646 patients. *Am J Orthop* 6:72–78
 19. Itoh M, Montemayor JS Jr, Matsumoto E, Eason A, Lee MH, Folk FS (1991) Accelerated wound healing of pressure ulcers by pulsed high-peak power electromagnetic energy (Diapulse). *Decubitus* 4(24–25):29–34
 20. Salzberg CA, Cooper-Vastola SA, Perez F, Viehbeck MG, Byrne DW (1995) The effects of nonthermal pulsed electromagnetic energy on wound healing of pressure ulcers in spinal cord-injured patients: a randomized, double-blind study. *Ostomy Wound Manage* 41:42–44, 46, 48 passim
 21. Stiller MJ, Pak GH, Shupack JL, Thaler S, Kenny C, Jondreau L (1992) A portable pulsed electromagnetic field (PEMF) device to enhance healing of recalcitrant venous ulcers: a double-blind, placebo-controlled clinical trial. *Br J Dermatol* 127:147–154
 22. Fletcher S (2011) Successful treatment of venous stasis ulcers with combination compression therapy and pulsed radiofrequency energy in a patient scheduled for amputation. *J Wound Ostomy Cont Nurs* 38:91–94
 23. Frykberg R, Martin E, Tallis A, Tierney E (2011) A case history of multimodal therapy in healing a complicated diabetic foot wound: negative pressure, dermal replacement, and pulsed radiofrequency energy therapies. *Int Wound J* 8:132–139
 24. Frykberg RG, Driver VR, Lavery LA, Armstrong DG, Isenberg RA (2011) The use of pulsed radiofrequency energy therapy in treating lower extremity wounds: results of a retrospective study of a wound registry. *Ostomy Wound Manage* 57:22–29
 25. Rawe IM, Vlahovic TC (2011) The use of a portable, wearable form of pulsed radiofrequency electromagnetic energy device for the healing of recalcitrant ulcers: a case report. *Int Wound J*. doi: [10.1111/j.1742-481X.2011.00853.x](https://doi.org/10.1111/j.1742-481X.2011.00853.x)
 26. Heden P, Pilla AA (2008) Effects of pulsed electromagnetic fields on postoperative pain: a double-blind randomized pilot study in breast augmentation patients. *Aesthet Plast Surg* 32:660–666
 27. Rohde C, Chiang A, Adipoju O, Casper D, Pilla AA (2010) Effects of pulsed electromagnetic fields on IL-1 beta and post-operative pain: a double-blind, placebo-controlled pilot study in breast reduction patients. *Plast Reconstr Surg* 125:1620–1629
 28. Strauch B, Herman C, Dabb R, Ignarro LJ, Pilla AA (2009) Evidence-based use of pulsed electromagnetic field therapy in clinical plastic surgery. *Aesthet Surg J* 29:135–143
 29. Li Q, Kao H, Matros E, Peng C, Murphy GF, Guo L (2011) Pulsed radiofrequency energy (PRFE) accelerates wound healing in diabetic mice. *Plast Reconstr Surg* 127:2255–2262
 30. Moffett J, Griffin N, Ritz M, George F (2010) Pulsed radiofrequency energy field treatment of cells in culture results in increased expression of genes involved in the inflammation phase of lower extremity diabetic wound healing. *J Diabet Foot Complicat* 2:57–64
 31. Williamson A, Hoggart B (2005) Pain: a review of three commonly used pain rating scales. *J Clin Nurs* 14:798–804
 32. White PF, Kehlet H (2010) Improving postoperative pain management: what are the unresolved issues? *Anesthesiology* 112:220–225
 33. Gilron I, Orr E, Tu D, Mercer CD, Bond D (2009) A randomized, double-blind, controlled trial of perioperative administration of gabapentin, meloxicam, and their combination for spontaneous and movement-evoked pain after ambulatory laparoscopic cholecystectomy. *Anesth Analg* 108:623–630
 34. White PF, Sacan O, Tufanogullari B, Eng M, Nuangchamngong N, Ogunnaike B (2007) Effect of short-term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. *Can J Anaesth* 54:342–348
 35. Bentall RHC (1986) Low-level pulsed radiofrequency fields and the treatment of soft tissue injuries. *Bioelectrochem Bioenerg* 16:531–548

The use of a portable, wearable form of pulsed radio frequency electromagnetic energy device for the healing of recalcitrant ulcers: a case report

Ian M Rawe, Tracey C Vlahovic

Rawe IM, Vlahovic TC. The use of a portable, wearable form of pulsed radio frequency electromagnetic energy device for the healing of recalcitrant ulcers: a case report. *Int Wound J* 2011; doi: 10.1111/j.1742-481X.2011.00853.x

ABSTRACT

Pulsed radio frequency energy (PRFE) has successfully been used to treat diabetic and venous stasis ulcers. In this case report, a lightweight wearable form of a PRFE device was evaluated and used to treat three diabetic foot ulcers and one venous stasis ulcer. The ulcers were present on the four patients for more than 3 months and had failed to heal after conventional treatment. A lightweight battery-powered, wearable form of PRFE device was introduced as a treatment and used 6–8 hours per day for a period of 6 weeks. All patients after 1 week of therapy showed improvement and wound size was seen to decrease. Patient 1 had a venous stasis ulcer, and reported significant pain relief after 2 weeks treatment. Patients 2 and 3 achieved complete healing after 3 weeks treatment, and patients 1 and 4 had a 95% and 88% reduction in wound size, respectively, after the 6-week study period. Both these patients continued to complete healing using the PRFE device after the 6-week study period. PRFE treatment delivered in the form of a wearable lightweight patch appears to offer promise in the treatment of recalcitrant chronic wounds.

Key words: Chronic • Device • Healing • PRFE • Wounds

INTRODUCTION

Diabetic foot ulcers are the most common chronic wounds in western industrialised

countries. Of the millions who have diabetes mellitus, 15% will suffer of foot ulceration which often leads to amputation (100, 000 per annum in the US alone). The economic burden of treating diabetes as its associated complications is extreme (1) and will likely increase as the rate of diabetes continues to rise. Statistics from the American Diabetes Association show the prevalence of diabetes at 25.8 million children and adults, or 8.3% of the US population.

Authors: IM Rawe, PhD, Bioelectronics Corporation, Frederick, MD, USA; TC Vlahovic, DPM, Temple University School of Podiatric Medicine, Philadelphia, PA, USA

Address for correspondence: IM Rawe, PhD, BioElectronics Corporation, 4539 Metropolitan Ct, Frederick, MD 21704, USA

E-mail: ian.rawe@gmail.com

Key Points

- electrotherapy in the form of pulsed radio frequency electromagnetic (PRFE) energy has recently received a new focus, with a number of case reports showing promising results in the healing of chronic wounds
- however, there are still major limitations to PRFE devices, as treatment regimens require 2×30 minute treatments per day, making it impractical for most ambulatory patients, restricting its use to severe chronic wounds
- in this case report, we show the application of a wearable battery-powered form of PRFE device for the treatment of recalcitrant wounds
- the lower energy levels emitted by this form of PRFE device are compensated by extended use times
- the PRFE device used in this case study was ActiPatch™ (BioElectronics Corporation, Frederick, MD) which delivers PRFE at a carrier frequency of 27.12 MHz and a pulse rate of 1000 Hz
- at the Temple University Foot and Ankle Institute, four adult African-American diabetic males between the ages of 40 and 75 with ulcers present for longer than 3 months were admitted into the pilot study

Venous stasis ulcers are a major cause of chronic wounds, and are typically associated with significant pain. Venous stasis ulcers are common in patients who have a history of leg swelling, varicose veins, or a history of blood clots in either the superficial or the deep veins of the legs. Venous ulcers is the most common aetiology of lower extremity ulceration, affecting approximately 1% of the US population (2).

The healing of diabetic foot ulcers, is necessary for the prevention of amputation and a number of advanced technologies have been introduced to achieve higher success in amputation prevention and limb preservation (3). Electrotherapy in the form of pulsed radio frequency electromagnetic (PRFE) energy has recently received a new focus, with a number of case reports showing promising results in the healing of chronic wounds (4–8). A retrospective study on the Regeneration Wound Healing Registry (Regeneration Biomedical, Scottsdale, AZ) has indicated that PRFE therapy holds promise to be an effective treatment for chronic wounds (9). Regeneration Biomedical's Provant System is a suitcase-sized device that emits non-ionising, radio frequency energy at 27.12 MHz. There is a growing list of clinical studies that have shown the safety and efficacy of PRFE as a therapy, as has been recently reviewed by Guo *et al.* (10). However, there are still major limitations to PRFE devices, as treatment regimens require 2×30 minute treatments per day, making it impractical for most ambulatory patients, restricting its use to severe chronic wounds.

In this case report, we show the application of a wearable battery-powered form of PRFE device for the treatment of recalcitrant wounds. The lower energy levels emitted by this form of PRFE device are compensated by extended use times. The PRFE device used in this case study was ActiPatch™ (BioElectronics Corporation, Frederick, MD) which delivers PRFE at a carrier frequency of 27.12 MHz and a pulse rate of 1000 Hz.

MATERIALS AND METHODS

At the Temple University Foot and Ankle Institute, four adult African-American diabetic males between the ages of 40 and 75 with ulcers present for longer than 3 months were admitted into the pilot study. Three patients had diabetic neuropathic ulcers and one had

a venous stasis ulcer. All the diabetic ulcer patients had at least one palpable pedal pulse and an ulcer of Wagner Grade II or higher.

All ulcers had previously been treated with a variety of methods, without appreciable healing, and are described for each patient. Patient 1 was 72 years old with type II diabetes that had a venous stasis ulcer that had undergone multi-layer compression therapy for 4 weeks without any appreciable healing. Significant pain was experienced by this patient who was assessed by a 0–10 point visual analogue scale (VAS). Patient 2 was 42 years old with type II diabetes and an actively working truck driver. Previous failed treatment included wound debridement, use of Promogran matrix and dry sterile dressing. Once the PRFE device was added to the regimen, Promogran was discontinued. Patient 3 was a 62-year-old patient with insulin-controlled diabetes that had not responded to debridement and application of triple antibiotic ointment with offloading. Once the PRFE device was added, triple antibiotic was discontinued. Patient 4 was a 74-year-old patient with insulin-controlled diabetes presented with a right heel decubitus ulcer that resulted following hospitalisation for prostate surgery. He had already had a below knee amputation on the left side. The right heel wound was granular and non-infected. Offloading with a protective boot and wound care consisting of debridement, Promogran matrix and dry sterile dressings were done prior to the PRFE device use. Once the PRFE device was used, weekly debridement and offloading was maintained. After informed consent, patients adopted a protocol that used the PRFE device for 6–8 hours per day. The patients with diabetic ulcers had their wounds covered with moist saline gauze, ActiPatch™, and a dry sterile dressing. When the ActiPatch™ PRFE device was not in use, the ulcer was covered with moist saline gauze and dry sterile dressing. Compression therapy was continued with patient 1 along with the PRFE device for 6–8 hours per day. Patients kept a journal of their PRFE device use and brought the log in during their weekly visits. Weekly visits consisted of sharp debridement and surgical scrub, for the diabetic ulcer patients, followed by measurement and photographic documentation. Wounds were evaluated for any signs of infection and new changes such as increased depth or drainage. The PRFE device was also evaluated for proper functioning at

each visit. Patients were educated on their daily wound dressing changes. The wounds were evaluated once weekly for a total of 6 weeks.

RESULTS

The patients tolerated the PRFE therapy well and reported no negative side effects. The diabetic ulcers still needed to be sharply debrided on a weekly basis, but patients were pleased with the therapy and its ease of use at home. Table 1 contains the patient age, wound location and wound measurements in centimeters at the start of the treatment (week 0) and for the following 6 weeks of treatment on a weekly basis. Starting at week 1, all patients were seen to have a decrease in wound size. The ulcers had a steady decrease in size to side closure and in visible periwound oedema. Patients 2 and 3 had complete healing of their diabetic ulcers after 3 weeks of treatment.

Patient 1 had a venous stasis ulcer, as shown in Figure 1, which caused the patient significant pain. After 2 weeks of PRFE therapy the patient reported significant pain relief. The ulcer of patient 1 decreased in size from 4×2.5 cm to 0.7×0.5 cm at the end of the 6-week study period, a decrease of approximately 95% of the wound area. The venous stasis ulcer continued to complete healing after the study period with continued use of the PRFE therapy device.

The right foot ulcer of patient 2 is shown in Figure 2 and the left heel ulcer of patient 3 is shown in Figure 3. Both ulcers of patients 2 and 3 improved rapidly with PRFE treatment, recovering up to 50% of the wound area after 1 week of PRFE treatment. The ulcers progressed to complete healing after 3 weeks of PRFE treatment.

The diabetic ulcer of patient 4 had a wound size at the beginning of treatment of 2.5×1.75 cm, by week 4 this had decreased to 1×1 cm, approximately a 73% reduction in size and by week 6 the wound area decreased to

1×0.5 cm, a reduction of 88% in size. Wound area reduction at weeks 1 and 4 is a strong indicator of complete healing (11). Patient 4 had significant reduction in wound size at week 6 and continued on to healing after the study period, using the PRFE treatment.

DISCUSSION

The mechanism by which PRFE promotes the healing of chronic wounds is not fully understood. But studies on cells and animals have given insight into the effects of PRFE therapy. Upregulation of gene families involved in tissue repair in co-cultures of human dermal fibroblasts and epidermal keratinocytes treated with PRFE has been shown (12). These included metalloproteinase and tissue inhibitor of metalloproteinase, interleukin-related genes, interferon-related genes and tumour necrosis factor-related genes. Cell studies have demonstrated a upregulation of fibroblast growth factor-2 (FGF-2) after PRFE exposure, an important molecule in wound healing for promoting endothelial cell proliferation, angiogenesis and granulation tissue formation. PRFE therapy given to animal wound models of diabetes have reported to an upregulation of FGF-2 (13), increased wound healing and wound tensile strength compared to sham control animals (14,15).

A portable wearable PRFE device was first used in 1982 for the treatment of postoperative wounds following blepharoplasty (16). A study by Stiller *et al.*, using a wearable form of PRFE device evaluated its clinical efficacy and safety in a placebo-controlled multicenter trial. Significant decreases in wound depth and pain intensity favouring the active group were seen, wounds after 8 weeks of treatment in the active group had a 47.7% decrease in wound surface area versus a 42.3% increase for placebo (17). The device used in this study weighed 505 g and was

Key Points

- the mechanism by which PRFE promotes the healing of chronic wounds is not fully understood
- PRFE therapy given to animal wound models of diabetes have reported to an upregulation of FGF-2, increased wound healing and wound tensile strength compared to sham control animals
- the device used in this study weighed 505 g and was used 3 hours per day

Table 1 The patient age, ulcer location and ulcer size data (in centimeters) of each patient at week 0 (start of treatment) and for each week of the 6-week study period

Patient	Age	Location	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
1	66	Right leg	4×2.5	4×2.3	4×2	3×1.5	2×1.5	1×0.7	0.7×0.5
2	60	Right foot	0.5×0.5	0.3×0.3	0.2×0.1	ulcer healed			
3	43	Left heel	4×1	2×0.5	1×0.3	ulcer healed			
4	74	Right heel	2.5×1.75	2×2	2×1.5	1.7×0.7	1×1	1×0.5	1×0.5



Figure 1. The venous stasis ulcer of patient 1 is shown at weeks 0, 2, 4 and 6 of PRFE treatment. Significant pain relief was reported by the patient after 2 weeks treatment. The ulcer had decreased in size from 4.0×2.5 cm to 0.7×0.5 cm after 6 weeks PRFE treatment. The ulcer continued onto healing using the PRFE therapy.

Key Points

- in this pilot study, a light weight wearable form of PRFE, ActiPatch™, was used to facilitate the wound healing process in both diabetic and venous stasis lower extremity ulcers
- the PRFE device used in this case study was in the form a patch and was easy to use from both the physician's and patient's standpoint
- since the completion of this study, ActiPatch™ has been refined and updated, and now consists of a small control module and a 12 cm or 8 cm antenna and weighs approximately 8 g
- the reconfigured device is now used as a 24-hour continuous PRFE therapy with the same carrier frequency of 27.12 MHz and 1000 Hz pulse rate

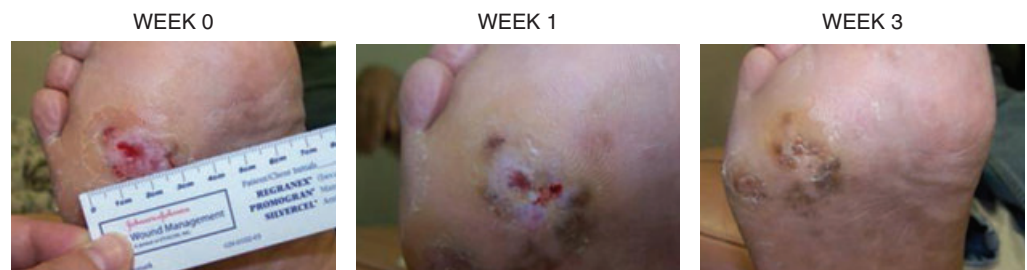


Figure 2. Patient 2 had a 0.5×0.5 cm diabetic ulcer at the beginning of PRFE treatment, which healed after 3 weeks PRFE therapy. The ulcer at weeks 0, 1 and 3 is shown.

used 3 hours per day. More recently clinical trials on the postoperative recovery after breast augmentation surgery (18) and breast reduction surgery (19) have clearly demonstrated the control of postoperative pain with newer versions of wearable, portable PRFE devices.

In this pilot study presented here, a light weight wearable form of PRFE, ActiPatch™, was used to facilitate the wound healing process in both diabetic and venous stasis lower

extremity ulcers. The PRFE device used in this case study was in the form a patch and was easy to use from both the physician's and patient's standpoint. Since the completion of this study, ActiPatch™ has been refined and updated, and now consists of a small control module and a 12 cm or 8 cm antenna and weighs approximately 8 g. The reconfigured device is now used as a 24-hour continuous PRFE therapy with the same carrier frequency of 27.12 MHz



Figure 3. Patient 3 had a 4.0×1 cm diabetic ulcer on the left heel. After 3 weeks of PRFE treatment the ulcer had completely healed. The ulcer is shown at weeks 0, 1, 2 and 3.

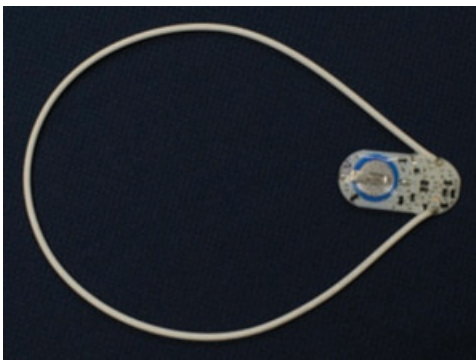


Figure 4. The latest version of the PRFE device is shown, consisting of a small control module and a wire antenna, either 12 cm or 8 cm. The PRFE device is used 24 hours per day, is lightweight weighing approximately 8 g and provides treatment continuously for 7 days.

and 1000 Hz pulse rate. Figure 4 shows the latest version of the PRFE device and Figure 5 shows the application of the PRFE device on a patient with a venous stasis ulcer; prior to PRFE therapy this patient was considered for



Figure 5. A version of the PRFE device is shown in use on a patient with a venous stasis ulcer.

amputation, however, the ulcer healed within 8 weeks and the patient avoided amputation (unpublished data).

The results from this pilot study suggest that lightweight wearable PRFE devices maybe an effective adjunct therapy for recalcitrant wounds promoting healing and reducing pain. The ease of use, low cost and compatibility with

Key Points

- the results from this pilot study suggest that lightweight wearable PRFE devices maybe an effective adjunct therapy for recalcitrant wounds promoting healing and reducing pain

Key Points

- the ease of use, low cost and compatibility with current conventional therapy also suggest this form of wearable PRFE device could be widely applied as a first choice therapy, although further studies are required to determine their true value

current conventional therapy also suggest this form of wearable PRFE device could be widely applied as a first choice therapy, although further studies are required to determine their true value.

REFERENCES

- Driver VR, Fabbi M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. *J Am Podiatr Med Assoc* 2010;100:335–41.
- Collins L, Seraj S. Diagnosis and treatment of venous ulcers. *Am Fam Physician* 2010;81:989–96.
- Wu SC, Marston W, Armstrong DG. Wound care: the role of advanced wound healing technologies. *J Vasc Surg* 2010;52 Suppl 3:59S–66S.
- Larsen JA, Overstreet J. Pulsed radio frequency energy in the treatment of complex diabetic foot wounds: two cases. *J Wound Ostomy Continence Nurs* 2008;35:523–7.
- Porreca EG, Giordano-Jablon GM. Treatment of severe (Stage III and IV) chronic pressure ulcers using pulsed radio frequency energy in a quadriplegic patient. *Eplasty* 2008;8:e49.
- Fletcher S. Successful treatment of venous stasis ulcers with combination compression therapy and pulsed radio frequency energy in a patient scheduled for amputation. *J Wound Ostomy Continence Nurs* 2011;38:91–4.
- Frykberg R, Martin E, Tallis A, Tierney E. A case history of multimodal therapy in healing a complicated diabetic foot wound: negative pressure, dermal replacement and pulsed radio frequency energy therapies. *Int Wound J* 2011;8:132–9.
- Maier M. Pulsed radio frequency energy in the treatment of painful chronic cutaneous wounds: a report of two cases. *Pain Med* 2011;12:829–32.
- Frykberg RG, Driver VR, Lavery LA, Armstrong DG, Isenberg RA. The use of pulsed radio frequency energy therapy in treating lower extremity wounds: results of a retrospective study of a wound registry. *Ostomy Wound Manage* 2011;57:22–9.
- Guo L, Kubat NJ, Isenberg RA. Pulsed radio frequency energy (PRFE) use in human medical applications. *Electromagn Biol Med* 2011;30:21–45.
- Lavery LA, Barnes SA, Keith MS, Seaman JW Jr, Armstrong DG. Prediction of healing for post-operative diabetic foot wounds based on early wound area progression. *Diabetes Care* 2008;31:26–9.
- Moffett J, Griffin N, Ritz M, George F. Pulsed radio frequency energy field treatment of cells in culture results in increased expression of genes involved in the inflammation phase of lower extremity diabetic wound healing. *J Diabet Foot Complicat* 2010;2:57–64.
- Callaghan MJ, Chang EI, Seiser N, Aarabi S, Ghali S, Kinnucan ER, Simon BJ, Gurtner GC. Pulsed electromagnetic fields accelerate normal and diabetic wound healing by increasing endogenous FGF-2 release. *Plast Reconstr Surg* 2008;121:130–41.
- Goudarzi I, Hajizadeh S, Salmani ME, Abrari K. Pulsed electromagnetic fields accelerate wound healing in the skin of diabetic rats. *Bioelectromagnetics* 2010;31:318–23.
- Li Q, Kao H, Matros E, Peng C, Murphy GF, Guo L. Pulsed radio frequency energy (PRFE) accelerates wound healing in diabetic mice. *Plast Reconstr Surg* 2011;127:2255–62.
- Nicolle FV, Bental RM. Use of radio-frequency pulsed energy in the control of postoperative reaction in blepharoplasty. *Aesthetic Plast Surg* 1982;6:169–71.
- Stiller MJ, Pak GH, Shupack JL, Thaler S, Kenny C, Jondreau L. A portable pulsed electromagnetic field (PEMF) device to enhance healing of recalcitrant venous ulcers: a double-blind, placebo-controlled clinical trial. *Br J Dermatol* 1992;127:147–54.
- Heden P, Pilla AA. Effects of pulsed electromagnetic fields on postoperative pain: a double-blind randomized pilot study in breast augmentation patients. *Aesthetic Plast Surg* 2008;32:660–6.
- Rohde C, Chiang A, Adipoju O, Casper D, Pilla AA. Effects of pulsed electromagnetic fields on interleukin-1 beta and postoperative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients. *Plast Reconstr Surg* 2010;125:1620–9.

PULSED RADIOFREQUENCY ELECTROMAGNETIC FIELD THERAPY IS AN EFFECTIVE WOUND PAIN THERAPY

Ian M Rawe Ph.D¹, Randall Eldridge², Tracey Vlahovic DPM², Geert Vanwellegham³

1. BioElectronics Corporation, Frederick, Maryland, USA
2. Temple University School of Podiatric Medicine, Philadelphia, Pennsylvania, USA
3. CNS Wound, decubitus and prevention, H.-Hart Hospital Roeselare-Menen, Belgium

Introduction

Cutaneous skin ulcers, which can arise from a number of causes are often associated with a high level of persistent wound pain. Wound pain is often overlooked but studies have demonstrated high prevalence in most chronic wounds. Persistent pain places a further burden on patients who are already dealing with a complex chronic wound. Wound pain can lead to high stress levels, reduced mobility, sleep deprivation, withdrawal and depression. Another significant factor of wound pain is the potential negative effect on wound healing which occurs through a number of mechanisms. These mechanisms include increased production of stress hormones, cortisol and vasopression, which decrease immune function and thereby increasing infection rates. Pain mediators have now been directly linked to inflammation, whereby unresolved pain contributes directly to the chronic inflammation seen in many non-healing wounds.

Pulsed radiofrequency electromagnetic field therapy (PEMF) has been used to reduce pain in a number of medical conditions including orthopedic pain, arthritis pain and postoperative pain, and has been widely reported to improve wound healing. The purpose of this case series was to determine if a wearable form of PEMF therapy can reduce persistent wound pain.

Methods

Six subjects who had persistent wounds pain stemming from a variety of chronic wounds were placed on PEMF therapy. Treatment consisted of the addition of a wearable PEMF device, which was incorporated into or on top of the wound dressing. No other changes were made to the wound dressing protocol. The PEMF device uses a carrier frequency of 27.12Mhz , 1 khz pulse rate, and a pulse width of 100μsecs, delivering the electromagnetic energy into the tissue by a 12cm loop antenna. The device weighs 8g so adds no burden to the patient. The PEMF device operates for 10 days and was replaced weekly along with the wound dressing. Baseline pain (0 – 10 scale) was recorded along with weekly pain scores and progression to wound healing.

Results

No negative or adverse effects were noted with the addition of the wearable PEMF therapy. Persistent wound pain was significantly decreased or completely eliminated in all the cases. Pain levels reached a baseline by 1-2 weeks and were maintained at these levels. Of the six cases, four went from non-healing to closure, while Case 3 reduced in size by >50% and case 4 did not show improvement. The pain in the two cases that had not healed, both pyoderma cases, has been controlled for 10 months. All three pyoderma cases showed a reduction in wound drainage from moderate to low, and improvement to a 100% granular wound bed. There was also a noted decrease in pain levels at dressing change for all the cases.

Case	Chronic wound	Location	Duration	Pain VAS	VAS Pain + PEMF
1	Venous stasis	Lower leg	3 months	4	0
2	Pyoderma gangrenosum	Ankle & instep	2 years	5	0
3	Pyoderma gangrenosum	Ankle	3 years	4	0
4	Pyoderma gangrenosum	Heel	2 years	5	1
5	Venous stasis	Lower leg		7	0
6	Neurototic toe/amputation	Foot		7	0

Discussion

The addition of PEMF therapy in the form of a wearable device is an effective wound pain therapy and appears to have the additional ability to promote wound healing. Rapid wound healing was seen in four of the cases, while one case showed very slow, but progressive wound healing, and one case no wound closure. Persistent and intense pain can significantly interfere with a person's quality of life and general functioning and well-being. The elimination or significant reduction in wound pain in this case series indicated that PEMF could be of substantial benefit in improving patient quality of life. Research has shown that PEMF has an anti-inflammatory effect. Chronic inflammation is especially severe in pyoderma gangrenosum, usually requiring immunosuppression to achieve wound healing. However, resolution or a reduction of the underlying chronic inflammation in these pyoderma cases seems to have been resolved by treatment with the PEMF therapy.

Conclusion

PRFE therapy is a non-invasive, drug free therapy and has been shown to have an excellent safety profile. This case study series indicates that, as an adjunct therapy, wearable PEMF devices can be easily incorporated into wound dressing protocols and offer a simple effective method of controlling persistent wound pain and has potential to promote wound healing.

PULSED RADIOFREQUENCY ELECTROMAGNETIC FIELD: A POTENTIAL NOVEL THERAPY FOR DIABETIC PERIPHERAL NEUROPATHY PAIN

Ian M Rawe Ph.D¹, Sofia Neto², Perry Mayer MD²

1. BioElectronics Corporation, Frederick, Maryland, USA
2. The Mayer Institute, Hamilton, Ontario, Canada

Purpose

Diabetic peripheral neuropathy pain is a common complaint of diabetes mellitus and can result in extreme pain causing a significant impact on patient quality of life. Pulsed Radiofrequency electromagnetic field therapy has been used for controlling pain in a wide variety of medical applications. Pulsed electromagnetic fields have undergone limited clinical study for diabetic peripheral neuropathy pain with mixed results. Graavik et al 200, reported a reduction in pain and an improvement in nerve function with low frequency 600 and 800 Hz pulsed electromagnetic fields. However, a multi-centered trial using low frequency pulsed electromagnetic field failed to show improvement in pain scores but reported improvements in distal nerve density. Static magnets have been shown to have some success in reducing DPNP achieved with long term use (4 months). In this case study, we applied PEMF in the form of a wearable device, to assess the effect on pain levels in patients experiencing diabetic peripheral neuropathy pain.

Methods

Fourteen diabetic patients who were experiencing and who were being treated for long term neuropathy pain with >6 score on a 0-10 point visual analogue scale in their feet were recruited into the pilot study. Pain scores were scores that patients were experiencing under their current therapy and no changes were made to their current therapy after enrollment. The pulsed electromagnetic field device uses a carrier frequency of 27.12Mhz , 1 khz pulse rate, and a pulse width of 100μsecs, delivering the electromagnetic energy into the target tissue by a 12cm loop antenna.. The devices were attached with an adhesive patch to a sock which allowed for easily delivery of overnight therapy. Pain levels were assessed on an 11 point visual analogue pain scale (0 – 10) at baseline and after 6 weeks nightly pulsed electromagnetic field therapy.

Results

Of the 8 patients enrolled into the study five patients responded to the therapy. The average pain reduction was 40% or 3 VAS points for these five patients. Average pain prior to therapy was 7.4 VAS and average pain after six weeks nightly pulsed electromagnetic field therapy was 4.4 VAS points. A patient reported noticeable pain decrease was achieved in as little as 3-5 days and as long as 4 weeks. Maximum obtained pain decrease was reported to be from 1

week up to 8 weeks. The therapy has been adopted as standard therapy for the patients who received a clinically significant benefit. Long term use data will therefore become available.

Table 1. Pain levels prior to and post PEMF therapy with ActiPatch.

Case	Baseline VAS	Post-Treatment VAS	Reduction VAS/percent	Treatment time weeks	Weeks to record a pain reduction	Weeks to lowest pain level
1	8	4	4/50%	4	5 days	4
2	7	4	3/42%	6+	4	8
3	6	4	2/33%	6+	2	3-4
4	9	9	0	2		
5	7	4	3/42%	6+	3-4 days	2-3
6	9	6	3/33%	6+	1	1
7	8	8	0	3		
8	10	10	0	4		

Discussion

The results from this pilot study indicate the pulsed electromagnetic field treatment delivered by a lightweight wearable device has the potential to reduce diabetic peripheral neuropathy pain in a subset of patients. The 40% decrease in pain in responders is at clinically significant levels. Pulsed electromagnetic field in this form has the advantage of offering a therapy that has an extremely good safety profile, and to date, has no none adverse side effects. This allows for the adoption of this therapy as an adjunct therapy, and does not preclude the use of other therapies or systemic drug therapy. Further study is needed to determine if the analgesic effects of this therapy has potential to be synergistic with other current therapies, and or allow a reduction in quantity of systemic drugs used to control pain.

Conclusion

The results from this pilot study show pulsed electromagnetic field therapy delivered by a wearable device is able to significantly reduce the level of diabetic peripheral neuropathy pain in a subset of patients, further study is required.

Pulsed Radiofrequency Electromagnetic Field Therapy A Adjunct Wound Healing Therapy

Introduction

The use of pulsed radiofrequency electromagnetic field (PEMF), also termed (PRFE) therapy has shown notable success in healing of chronic wounds. PEMF is a non-ionizing energy at the shortwave radiofrequency band of the electromagnetic spectrum, commonly at a frequency of 27.12MHz. Since the introduction of PEMF in the 1950s, clinical studies on healing of chronic wounds(1-5) and surgical recovery(6, 7), as well orthopedic studies(8-11) have documented PEMF as a successful clinical therapy. A series of case reports (12-16) and a retrospective study on a wound registry(17) have re-introduced PEMF therapy as an adjunct wound healing therapy, as newer more portable PEMF devices have been introduced. Meta-analysis of the published clinical studies determined that PEMF therapy was statistically significant for wound healing outcomes, as well as pain and edema(18).

Known Downstream Biological Effects

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 show p42/44 MAP kinase activation(19), and increased cell proliferation. The MAP kinase family of intracellular signaling proteins is activated by a range of stimuli and the activated MAP kinase translocate to 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 which were studied by gene array demonstrated an up-regulation of gene families associated with all phases of the wound healing cycle(20, 21). These included many genes involved in the inflammatory stage of wound repair and expression of genes involved in angiogenesis and tissue remodeling.

In a mouse models of diabetes, wound healing rates were increased when exposed to PEMF, compared to animals that were sham PEMF treated(22). And 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.

PEMF Delivery

PEMF therapy is none invasive and is delivered through the wound dressing, and to date has shown no unwanted side effects. With positive reports in the literature documenting PEMF as an effective therapy, its wider adoption as an adjunct therapy seems warranted. However, limitations exist, that have restricted its adoption as a widely employed wound healing therapy. Current treatment regimens require 2 x 30 minute treatments per day and are delivered by clinic based, mains powered devices (figure1).



Considering that wounds, even in the healing phase can persist for weeks, this therapy appears to be impractical for most patients. The potential answer to this inherent limitation is portable lightweight wearable PEMF technology, which ideally could become be an integral part of the wound dressing as shown in Figure 2b and Figure 2c. Stiller et al 1992 (23), published a randomized control trial, in which a portable, wearable device to deliver the PEMF therapy was used. The portable device allowed for a home based treatment; in this case it was used for predominantly venous leg ulcers. The PEMF delivery device that was used, weighed 508g with treatment protocol consisting of 3 hrs per day. Significant decreases in wound area, wound depth, healthy granulation tissue and decreased pain intensity favoring the active group were seen. This study suggests that wearable, portable forms of PEMF could be an effective adjunct wounding healing therapy. Nicole and Bentall 1982 (24) were the first to publish a study using wearable battery powered extended use time PEMF device in which oedema and bruising were reportedly decreased following blepharoplasty. Bental, also published a paper documenting that extended use time wearable PEMF, reduced the healing time of experimental human skin wounds(25). Healing was shown to be 52 days in the untreated group compared to 39 days in the PEMF treated group. Histological analysis also showed advanced wound architecture, including near normal epidermal thickness in the treated wounds compared to a thin epidermis in the untreated wounds. More recent studies, using up to date technology have demonstrated the effectiveness of small wearable extended use time PEMF devices developed by BioElectronics. A significant reduction in postoperative pain in randomized, double blind placebo controlled studies has been reported (26-28). Plantar fasciitis, a recalcitrant heel pain has also been shown to be treated with portable, wearable extended use PEMF therapy(29). Given that postoperative pain is significantly controlled by wearable PEMF it

seems probable that chronic wounds can also be treated with these devices. Below is a series of case studies that have utilized RecoveryRx to induce wound healing in chronic wounds of various etiologies.

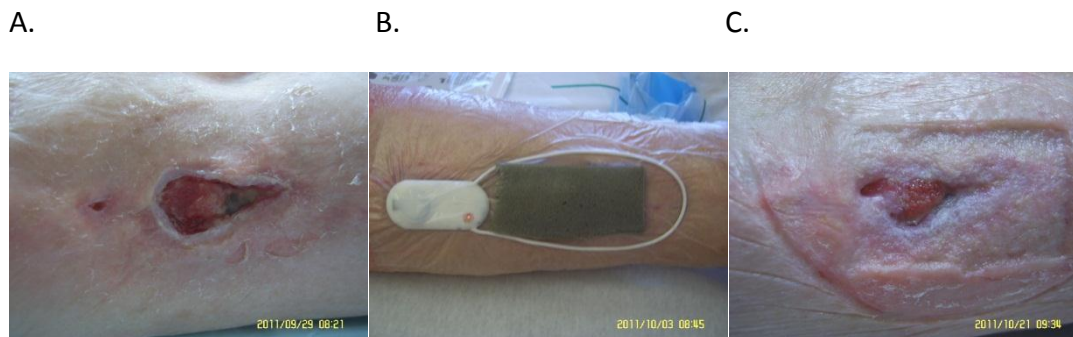
Design improvements to wearable portable devices suggest that they could become a standard in wound care given more successful clinical study. The modern devices are very small and lightweight (approximately 8 grams) and can easily be applied to most wound dressing protocols. For example Fig 1A shows a patient with a venous stasis leg ulcer and Fig 1B the wound dressing incorporating a PEMF device. Fig 1C shows the wound after 3 weeks of PEMF therapy. Fig 2A shows a patient with a substitute skin graft and Fig2B the wound dressing is shown along with the PEMF device. Fig 3C shows the wound after 19 days therapy.

Case Studies

Case Study 1

A left leg ulcer with exposed vascular prosthetic vein. Treatment consisted of debridement and 2 weeks of negative pressure wound therapy. After which the pulsed radiofrequency device was introduced with Polymem dressing. The leg ulcer reduced in size and was 50% reduced by 3 weeks of pulsed radiofrequency and Polymem dressing treatment. Wound went onto complete closure.

Figure 1 For example Fig 1A shows a patient with a venous stasis leg ulcer and Fig 1B the wound dressing incorporating a PEMF device. Fig 1C shows the wound after 3 weeks of PEMF therapy



Case Study 2

Patient 2 had ischemic right foot with quick evolution to necrotic toe. An urgent amputation was performed. The patient needed surgical debridement of necrotic wound edges after which negative pressure vacuum therapy was started and continued for 1 month. Split skin graft was used but an open wound was still left. PRFE therapy in combination with antiseptic Polymem silver was introduced. The split skin graft was successful and the remaining open wound healed with the combination of PRFE and Polymem silver dressing.

A.



B.



C.



References

1. Comorosan, S., Vasilco, R., Arghiropol, M., Paslaru, L., Jieanu, V., and Stelea, S. (1993) The effect of diapulse therapy on the healing of decubitus ulcer, *Rom J Physiol* 30, 41-45.
2. Goldin, J. H., Broadbent, N. R., Nancarrow, J. D., and Marshall, T. (1981) The effects of Diapulse on the healing of wounds: a double-blind randomised controlled trial in man, *Br J Plast Surg* 34, 267-270.
3. Itoh, M., Montemayor, J. S., Jr., Matsumoto, E., Eason, A., Lee, M. H., and Folk, F. S. (1991) Accelerated wound healing of pressure ulcers by pulsed high peak power electromagnetic energy (Diapulse), *Decubitus* 4, 24-25, 29-34.
4. Salzberg, C. A., Cooper-Vastola, S. A., Perez, F., Viehbeck, M. G., and Byrne, D. W. (1995) The effects of non-thermal pulsed electromagnetic energy on wound healing of pressure ulcers in spinal cord-injured patients: a randomized, double-blind study, *Ostomy Wound Manage* 41, 42-44, 46, 48 passim.
5. Tung, S., Khaski, A., Milano, E., and Kay, C. (1995) The application of Diapulse in the treatment of decubitus ulcers: case reports, *Contemp Surg* 47, 27-32.
6. Kaplan, E. G., and Weinstock, R. E. (1968) Clinical evaluation of diapulse as adjunctive therapy following foot surgery, *J Am Podiatry Assoc* 58, 218-221.
7. Aronofsky, D. H. (1971) Reduction of dental postsurgical symptoms using nonthermal pulsed high-peak-power electromagnetic energy, *Oral Surg Oral Med Oral Pathol* 32, 688-696.
8. Pennington, G. M., Danley, D. L., Sumko, M. H., Bucknell, A., and Nelson, J. H. (1993) Pulsed, non-thermal, high-frequency electromagnetic energy (DIAPULSE) in the treatment of grade I and grade II ankle sprains, *Mil Med* 158, 101-104.
9. Foley-Nolan, D., Barry, C., Coughlan, R. J., O'Connor, P., and Roden, D. (1990) Pulsed high frequency (27MHz) electromagnetic therapy for persistent neck pain. A double blind, placebo-controlled study of 20 patients, *Orthopedics* 13, 445-451.
10. Foley-Nolan, D., Moore, K., Codd, M., Barry, C., O'Connor, P., and Coughlan, R. J. (1992) Low energy high frequency pulsed electromagnetic therapy for acute whiplash injuries. A double blind randomized controlled study, *Scand J Rehabil Med* 24, 51-59.
11. Callaghan, M. J., Whittaker, P. E., Grimes, S., and Smith, L. (2005) An evaluation of pulsed shortwave on knee osteoarthritis using radioleucoscintigraphy: a randomised, double blind, controlled trial, *Joint Bone Spine* 72, 150-155.
12. Fletcher, S. (2011) Successful treatment of venous stasis ulcers with combination compression therapy and pulsed radio frequency energy in a patient scheduled for amputation, *J Wound Ostomy Continence Nurs* 38, 91-94.
13. Frykberg, R., Martin, E., Tallis, A., and Tierney, E. (2011) A case history of multimodal therapy in healing a complicated diabetic foot wound: negative pressure, dermal replacement and pulsed radio frequency energy therapies, *Int Wound J* 8, 132-139.
14. Larsen, J. A., and Overstreet, J. (2008) Pulsed radio frequency energy in the treatment of complex diabetic foot wounds: two cases, *J Wound Ostomy Continence Nurs* 35, 523-527.
15. Porreca, E. G., and Giordano-Jablon, G. M. (2008) Treatment of severe (Stage III and IV) chronic pressure ulcers using pulsed radio frequency energy in a quadriplegic patient, *Eplasty* 8, e49.

16. Maier, M. (2011) Pulsed radio frequency energy in the treatment of painful chronic cutaneous wounds: a report of two cases, *Pain Med* 12, 829-832.
17. Frykberg, R. G., Driver, V. R., Lavery, L. A., Armstrong, D. G., and Isenberg, R. A. (2011) The Use of Pulsed Radio Frequency Energy Therapy in Treating Lower Extremity Wounds: Results of a Retrospective Study of a Wound Registry, *Ostomy Wound Manage* 57, 22-29.
18. Guo, L., Kubat, N. J., Nelson, T. R., and Isenberg, R. A. (2012) Meta-analysis of clinical efficacy of pulsed radio frequency energy treatment, *Ann Surg* 255, 457-467.
19. Gilbert, T. L., Griffin, N., Moffett, J., Ritz, M. C., and George, F. R. (2002) The Provant® Wound Closure System Induces Activation of p44/42 MAP Kinase in Normal Cultured Human Fibroblasts, *Ann. N.Y. Acad. Sci.* 961, 168-171.
20. Moffett, J., Griffin, N. E., Ritz, M. C., and George, F. R. (2010) Pulsed radio frequency energy field treatment of cells in culture results in increased expression of genes involved in the inflammation phase of lower extremity diabetic wound healing., *The Journal of Diabetic Foot Complications* 2, 57-64.
21. Moffett, J., Kabut, N. J., Griffin, N. E., Ritz, M. C., and George, F. R. (2011) Pulsed radio frequency energy field treatment of cells in culture: Increased expression of genes involved in angiogenesis and tissue remodeling during wound healing., *The Journal of Diabetic Foot Complications* 3, 30-39.
22. Li, Q., Kao, H., Matros, E., Peng, C., Murphy, G. F., and Guo, L. (2011) Pulsed Radio Frequency Energy (PRFE) Accelerates Wound Healing In Diabetic Mice, *Plast Reconstr Surg*.
23. Stiller, M. J., Pak, G. H., Shupack, J. L., Thaler, S., Kenny, C., and Jondreau, L. (1992) A portable pulsed electromagnetic field (PEMF) device to enhance healing of recalcitrant venous ulcers: a double-blind, placebo-controlled clinical trial, *Br J Dermatol* 127, 147-154.
24. Nicolle, F. V., and Bentall, R. M. (1982) Use of radio-frequency pulsed energy in the control of postoperative reaction in blepharoplasty, *Aesthetic Plast Surg* 6, 169-171.
25. Bentall, R. H. C. (1986) Low-level pulsed radiofrequency feilds and the treatment of soft-tissue injuries, *Bioelectrochemistry and Bioenergetics* 16, 531-548.
26. Heden, P., and Pilla, A. A. (2008) Effects of pulsed electromagnetic fields on postoperative pain: a double-blind randomized pilot study in breast augmentation patients, *Aesthetic Plast Surg* 32, 660-666.
27. Rawe, I. M., Lowenstein, A., Barcelo, C. R., and Genecov, D. G. (2011) Conrol of postoperative pain with a wearable continuously operating pulsed radio frequency energy device - A preliminary study, *Aesthetic Plast Surg inpress*.
28. Rohde, C., Chiang, A., Adipoju, O., Casper, D., and Pilla, A. A. (2010) Effects of pulsed electromagnetic fields on interleukin-1 beta and postoperative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients, *Plast Reconstr Surg* 125, 1620-1629.
29. Brooke, J., Dauphinee, D. M., Korpinen, J., and Rawe, I. M. (2012) Pulsed Radio Frequency Electromagnetic Field Therapy: A Potential Novel Treatment for Plantar Fasciitis, *J Foot Ankle Surg in press*.

Pyoderma gangrenosum: pulsed radiofrequency therapy an effective pain and wound healing therapy: A three patient case series

Tracey Vlahovic DPM¹, Randall Eldridge¹, Ian M Rawe Ph.D²

1. Temple University School of Podiatric Medicine, Philadelphia, Pennsylvania, USA.
2. Bioelectronics Corporation, Frederick , Maryland

Author Contributions: All authors had full access to all the data in the report and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Vlahovic, Rawe Acquisition of data: Vlahovic, Eldridge Analysis and interpretation of data: Vlahovic, Eldridge, Rawe Drafting of the manuscript: Vlahovic, Rawe Critical revision of the manuscript for important intellectual content: Vlahovic, Rawe Study supervision: Vlahovic

.

Financial Disclosure: T Vlahovic none reported: Randall Eldridge none reported: Ian Rawe is paid employee of BioElectronics Corporation

BioElectronics donated the medical devices used in this case study

Corresponding authors:

Ian Rawe

BioElectronics Corporation

4539 Metropolitan Ct.

Frederick, MD 21704

Email: ian.rawe@gmail.com

Background

Pyoderma gangrenosum is a difficult to treat, neutrophilic dermatosis of skin and subcutaneous tissue characterized by a painful and progressive necrotizing process resulting in skin ulceration. Pulsed electromagnetic field therapy has shown to be an effective wound healing and pain therapy. Pulsed electromagnetic field therapy was used added to the treatment protocol of three cases of long standing pyoderma gangrenosum ulcers.

Observation

Three cases with long standing pyoderma gangrenosum ulcers, two at 2 years and one 3 years were placed on pulsed radiofrequency electromagnetic field (PEMF) therapy. The PEMF therapy was delivered by a wearable battery powered device that was used continuously 24 hrs per day, and incorporated in, or over the wound dressing. No other changes to the wound dressing protocol were made. Wound size was recorded at the beginning of PEMF therapy as was pain, recorded with a visual analogue scale of 0 -10. All cases reported a rapid resolution of their wound pain within 2 weeks of beginning PEMF therapy. One case who presented with two ulcers moved rapidly into wound healing and both ulcers healed in 11 weeks. A second case had a 50% wound size reduction after 8 months therapy. The third case showed an improvement in the wound bed forming a 100% red granular base from a 50% yellow/50% red base. Wound pain was consistently controlled in all three cases.

Conclusions

PEMF in a wearable form is very effective at controlling chronic wound pain and promoting healing of patients with pyoderma gangrenosum ulcers.

Pyoderma Gangrenosum (PG) is a rare neutrophilic dermatosis of skin and subcutaneous tissue characterized by a painful and progressive necrotizing process, with the lower leg as the most common location. The ulcers start with sterile pustules that progress into often extremely painful ulcers. The incidence in the USA is approximately 1 in 100,000. PG is often associated by a wide array of systemic disorders including rheumatoid arthritis and Crohn's disease¹. Treatment and management often centers around systemic drug therapy, including corticosteroids and immunosuppressants, either alone or in combination². Tumor necrosis factor inhibitors such as infliximab have shown some success in treating pyoderma gangrenosum, especially in people who have associated inflammatory bowel disease³.

Cutaneous skin ulcers, which can arise from a number of causes are often associated with a high level of pain. High levels of pain place a further burden on cases who are already dealing with a complex chronic wound. Wound pain can lead to reduced mobility, depression, loss of sleep and depression⁴. Another significant factor of wound pain is the potential negative effect on wound healing⁵.

Pulsed radiofrequency electromagnetic field (PEMF) therapy has been widely reported to reduce pain in a variety of medical conditions including orthopedic pain, arthritis pain and postoperative pain and has been comprehensively reviewed by Guo et al 2011⁶. PEMF therapy is non-invasive, drug free and to date there has been no reports of adverse side-effects. PEMF has also been used as a successful adjunct therapy for promoting wound healing⁷⁻¹⁴. Though, most PEMF therapy applications have consisted of clinic based machines, delivering the radiofrequency electromagnetic field through an applicator into the target soft tissue. These treatments are short, but with relatively high amounts of energy. However, daily or multiple treatments are needed to produce a therapeutic effect. Development of wearable, miniaturized medical devices that deliver PEMF therapy, that can be used for extended periods, up to 24 hrs per day, have now been reported to be effective pain control and healing modality for postoperative pain¹⁵⁻¹⁷, chronic wounds¹⁸ and orthopedic pain¹⁹.

In this case report we have applied wearable PEMF (RecoveryRX, Bioelectronics, Frederick MD) as a therapy for pyoderma gangrenosum to three cases with long standing (2-3 years) ulcers that had associated persistent chronic pain. PEMF therapy has the potential to benefit patients experiencing painful chronic ulcers in two ways, the reduction in wound pain and the promotion of tissue healing.

Observations

At the Temple University Foot and Ankle Institute (Philadelphia, USA), three adult cases who had long standing pyoderma gangrenosum ulcers which had been diagnosed by emission of other probable causes. After informed consent, cases adopted a protocol that utilized the PEMF device which was incorporated into the wound dressing protocol for each case. No other changes to the patients therapy were initiated. The device used in this study was a PEMF (RecoveryRx-BioElectronics Corp) device that emits a safe form of non-ionizing electromagnetic radiation. The carrier frequency is 27.12 MHz, an assigned FCC medical frequency, and has a pulse rate of 1000 pulses per second and 100 microsecond burst width. Peak burst output power of the 12 cm antenna is approximately 0.0098 watts covering a surface area of approximate 100 cm². The circuitry consists of low voltage (3 V) digital/analog electronics that control all timing functions to produce the therapeutic RF field, where the antenna field is placed directly above the therapeutic site. They are powered by a battery which enables functioning for a minimum of 7 days. The devices were replaced weekly along with the wound dressings. Wound size was recorded at the beginning of therapy and pain scores were assessed using a visual analogue scale (VAS) of 0 – 10 pts, with 0 being no pain, and 10 being extreme pain.

The case wound histories were as follows and summarized in table 1.

Table 1 Patient age, sex, ulcer location and duration along with baseline VAS pain.

Case	Age/sex	Ulcer location	Ulcer age (years)	VAS pain (0-10)
1	66 male	posterior ankle	3	5
2	57 male	right medial ankle	2	4
3	68 male	left dorsal midfoot	2	10
		medial heel/ankle	2	9

Case 1: Pyoderma ulcer was present on the left ankle of the patient for 3 years. Before addition of PEMF therapy the wound measured 6.7cm length x 4.0cm width x .2 cm depth. He had a moderate exudate with serous drainage. The wound base was 90% red and 10% yellow. The wound care protocol consisted of Silvercel® (Systagenix) antimicrobial dressing application and triple layer compression. The PG heel ulcer (figure 1) of has been treated for 8 months, the ulcer had an approximate surface area of 26.8cm² and a depth of 0.2 cm at the beginning of treatment. After 7 months the area had declined by 50% to 13.2cm² with a depth of 0.1cm. The wound is expected, with continued treatment to achieve complete closure. The wound bed formed a 100% red granular base and wound pain decreased to a VAS score of 1, and has been consistently maintained. Wound drainage has also decreased from moderate to low.

Figure 1 The pyoderma gangrenosum ulcer of case 1 was present for 3 years prior to introduction of PEMF therapy. (A) Shows ulcer prior to introduction of PEMF therapy, (B) 5 month of PEMF therapy and (C) 8 months. Persistent wound pain at beginning of treatment recorded a 5 point VAS score and was reduced to 1 with PEMF therapy.



Case 2: Pyoderma ulcer was present on the dorsal and distal side of the foot. The ulcers had been present for 2 years and failed systemic corticosteroid and immunosuppressant therapy. PEMF therapy was added to his wound care regimen of Bionect® (Innocutis) on the wound and desoximetasone .05% applied to the periwound area, and crushed dapsone (25 mg) was added to his care and applied directly to the ulcer. The wound base was 50% red and 50% yellow with moderate serous exudate and a VAS pain level of 4. On introduction of PEMF therapy wound pain declined to 0 within two weeks this has been maintained for 8 months. There was a change from the 50% red, 50% yellow wound bed to a 100% red granular wound bed (figure 2) and a decrease in serous exudate from moderate to low.

Figure 2 The pyoderma gangrenosum ulcer of case 2 went from a VAS score of 4 to 0 and the wound bed from (A) 50% yellow/50% red to (B) 100% granular red. Wound drainage was also reduced from moderate to low serous exudate. The ulcer has been treated for 8 months and has had consistent control of wound pain.

A



B



Case 3: pyoderma ulcer had a history of ulcerations and had two lesions: one on the left dorsal midfoot and the other on medial heel/ankle that had been present for 2 years. Therapy prior to PEMF therapy addition consisted of compression, curettage, Hydrofera Blue® (Hydrofera LLC), and topical silver sulfadiazine treatments. The left dorsal midfoot wound base was 80% red and 20% yellow with a moderate serosanguinous exudate. Medial heel ankle wound ulcer base was 80% red and 20% yellow with moderate serosanguinous drainage.

VAS pain for these ulcers was high recording 10 for the left dorsel midfoot ulcer and 9 for the medial heel/ankle ulcer. Vicodin was used for pain medication. For this case addition of PEMF therapy after 1 week moved both ulcers into wound healing (figure 3). Wound pain was reduced to VAS score of 0 and vicodin was no longer required. The ulcers of this case closed in 11 weeks after initiating PEMF therapy.

Figure 3A. The medial ankle pyoderma gangrenosum ulcer of case 3, shown at PEMF treatment time of (A) 0 weeks (B) at 2 weeks which shows a decrease in wound area (C) and 11 weeks at which the ulcer has closed. VAS pain was 9 at the start of treatment and reduced to 0 by 2 weeks and analgesic medication use was no longer required.



Figure 3B The dorsal pyoderma gangrenosum ulcer of case 3, shown at PEMF treatment time of (A) 0 weeks (B) at 2 weeks which shows a decrease in wound area (C) and 11 weeks at which the ulcer has closed. VAS pain was 10 at the start of treatment and reduced to 0 by 2 weeks and analgesic medication use was no longer required.

A



B



C



Note all the cases after control of the persistent wound was controlled, wound pain at dressing change was reduced to 0 on the VAS scale of the three cases.

Table 2. Wound size at beginning of PEMF therapy and current wound size along with duration of treatment

case	Size at start PEMF therapy	Current wound size	Duration of treatment
1	6.7cm length x 4.0cm width x 0.2 cm depth	6cm length x 2.2 cm width x .1 cm depth	8 months
2	8cm length x 5cm width x 0.1 cm depth	8.5cm x 5.4cm x .2cm	8 months
3	8cm length x 7 cm width x 0.1cm depth 6.8cm length x 4.5cm width x .1 cm depth	Healed healed	11 weeks 11 weeks

Comment

Of the three pyoderma cases presented in this report all had chronic long standing wounds that had a high level of associated persistent chronic wound pain. The addition of PEMF therapy in the form of a wearable device, which was used constantly, resulted in a rapid, and sustained reduction in wound pain. All three cases had resolution of wound pain by week 2, which was not dependent on healing of the wounds. Two cases have now been treated with PEMF therapy for 7 and 8 months, and wound pain has been consistently controlled. The decrease or elimination of the persistent chronic pain also resulted in wound dressing changes that were pain free, an important part of patient care.

PEMF therapy has been reported to promote wound healing as well as being an effective pain therapy in many clinical applications⁶. Meta-analysis of published clinical studies has shown PEMF therapy to be statistically significant in promoting wound healing, as well reducing pain and edema²⁰. Of the three pyoderma cases in this study 1 case with two ulcers on the left foot moved into the healing phase very rapidly, and both ulcers healed after 11 weeks of PEMF therapy. A second case with a heel ulcer has been under PEMF therapy for 7 months and has seen the wound area decrease by 50%. It is anticipated that continued PEMF will result in the complete healing of this ulcer. Case 2 has been treated for 8 months with no appreciable healing, however the wound bed has changed from a 50% yellow, 50% base to a 100% red granular base with low wound drainage. With pyoderma, surgery is not commonly used as a treatment option because trauma to the skin may worsen existing ulcers or stimulate new ones to develop. However, the apparent reduced inflammation in this case and generation of a 100% granular base may now make this case suitable for an artificial skin graft.

Most non-healing wounds fail to progress through the normal phases of wound repair, but instead remain in a chronic inflammatory state, and express high levels of inflammatory cytokines, proteases, and low levels of growth factors²¹. Chronic inflammation is especially severe in pyoderma gangrenosum, usually requiring immunosuppression to achieve wound healing. However, resolution or a reduction of the underlying chronic inflammation in these pyoderma cases seems to have been resolved by treatment with the PEMF therapy. Allowing for the progression of wound healing in two of the three cases, and an improvement in the wound bed in the third case. The potential effect of PEMF therapy on wound inflammation has been

reported. PEMF has been shown to reduce the expression of the cytokine interleukin 1 β from patients recovering from surgery¹⁷, suggesting a modulation of the inflammatory process. Using gene array on co-cultures of human dermal fibroblasts and human keratinocytes, which were exposed to a PEMF signal have shown up-regulation of genes in the inflammatory phase and the tissue repair phase of the wound healing cycle^{22, 23}. These reports suggest that PEMF therapy can influence the wound healing cycle by resolving inflammation and promoting tissue repair. The growth factor fibroblast growth factor-2 (FGF-2) has been reported to be up-regulated after PEMF exposure in cells²⁴ and in animal wound models²⁵. FGF-2 is an important molecule in wound healing for promoting endothelial cell proliferation, angiogenesis and granulation tissue formation.

Persistent and intense pain can significantly interfere with a person's quality of life and general functioning and well-being. Pain coupled to chronic non-healing wounds places an extra burden and increased suffering on these cases. Wound pain is also a substantial obstacle to wound healing through a variety of mechanisms²⁶ including the production of vasopressin and cortisol²⁷. PEMF has been previously reported to reduce wound pain in two cases with venous stasis wounds²⁸, using a higher power device. A study by Stiller et al 1993, using a wearable form of PEMF in a placebo controlled multicenter trial significantly decreased pain intensity²⁹ as well as promoting wound healing in cases with venous stasis ulcers. A number of case studies have shown that PEMF therapy is able to promote the healing of recalcitrant wounds^{8-10, 13, 14, 18, 28, 30}.

This case study series indicates that, as an adjunct therapy, wearable PEMF devices can be easily incorporated into wound dressing protocols and offer a simple effective method of controlling persistent wound pain in cases with pyoderma gangrenosum and potentially initiate wound healing. PEMF therapy is a non-invasive, drug free therapy and has been shown to have an excellent safety profile. These features of PEMF therapy will allow it to be used along standard systemic drug therapies recommended for the treatment of PG.

References

1. Reichrath J, Bens G, Bonowitz A, Tilgen W: Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients, *J Am Acad Dermatol* 2005, 53:273-283
2. Saracino A, Kelly R, Liew D, Chong A: Pyoderma gangrenosum requiring inpatient management: a report of 26 cases with follow up, *Australas J Dermatol* 2011, 52:218-221
3. Hayashi H, Kuwabara C, Tarumi K, Makino E, Fujimoto W: Successful treatment with infliximab for refractory pyoderma gangrenosum associated with inflammatory bowel disease, *J Dermatol* 2011,
4. Gottrup F, Jorgensen B, Karlsmark T, Sibbald RG, Rimdeika R, Harding K, Price P, Venning V, Vowden P, Junger M, Wortmann S, Sulcaite R, Vilkevicius G, Ahokas TL, Ettler K, Arenbergerova M: Reducing wound pain in venous leg ulcers with Biatain Ibu: a randomized, controlled double-blind clinical investigation on the performance and safety, *Wound Repair Regen* 2008, 16:615-625
5. Soon K, Acton C: Pain-induced stress: a barrier to wound healing, *Wounds UK* 2006, 2:92-101
6. Guo L, Kubat NJ, Isenberg RA: Pulsed radio frequency energy (PRFE) use in human medical applications, *Electromagn Biol Med* 2011, 30:21-45
7. Comorosan S, Vasilco R, Arghiropol M, Paslaru L, Jieanu V, Stelea S: The effect of diapulse therapy on the healing of decubitus ulcer, *Rom J Physiol* 1993, 30:41-45
8. Fletcher S: Successful treatment of venous stasis ulcers with combination compression therapy and pulsed radio frequency energy in a patient scheduled for amputation, *J Wound Ostomy Continence Nurs* 2011, 38:91-94
9. Frykberg R, Martin E, Tallis A, Tierney E: A case history of multimodal therapy in healing a complicated diabetic foot wound: negative pressure, dermal replacement and pulsed radio frequency energy therapies, *Int Wound J* 2011, 8:132-139
10. Frykberg RG, Driver VR, Lavery LA, Armstrong DG, Isenberg RA: The Use of Pulsed Radio Frequency Energy Therapy in Treating Lower Extremity Wounds: Results of a Retrospective Study of a Wound Registry, *Ostomy Wound Manage* 2011, 57:22-29

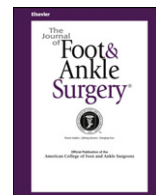
11. Goldin JH, Broadbent NR, Nancarrow JD, Marshall T: The effects of Diapulse on the healing of wounds: a double-blind randomised controlled trial in man, *Br J Plast Surg* 1981, 34:267-270
12. Itoh M, Montemayor JS, Jr., Matsumoto E, Eason A, Lee MH, Folk FS: Accelerated wound healing of pressure ulcers by pulsed high peak power electromagnetic energy (Diapulse), *Decubitus* 1991, 4:24-25, 29-34
13. Larsen JA, Overstreet J: Pulsed radio frequency energy in the treatment of complex diabetic foot wounds: two cases, *J Wound Ostomy Continence Nurs* 2008, 35:523-527
14. Porreca EG, Giordano-Jablon GM: Treatment of severe (Stage III and IV) chronic pressure ulcers using pulsed radio frequency energy in a quadriplegic patient, *Eplasty* 2008, 8:e49
15. Heden P, Pilla AA: Effects of pulsed electromagnetic fields on postoperative pain: a double-blind randomized pilot study in breast augmentation patients, *Aesthetic Plast Surg* 2008, 32:660-666
16. Rawe IM, Lowenstein A, Barcelo CR, Genecov DG: Control of postoperative pain with a wearable continuously operating pulsed radio frequency energy device - A preliminary study, *Aesthetic Plast Surg* 2011, inpress:
17. Rohde C, Chiang A, Adipoju O, Casper D, Pilla AA: Effects of pulsed electromagnetic fields on interleukin-1 beta and postoperative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients, *Plast Reconstr Surg* 2010, 125:1620-1629
18. Rawe IM, Vlahovic TC: The use of a portable, wearable form of pulsed radio frequency electromagnetic energy device for the healing of recalcitrant ulcers: A case report, *Int Wound J* 2011,
19. Brooke J, Dauphinee DM, Korpinen J, Rawe IM: Pulsed Radio Frequency Electromagnetic Field Therapy: A Potential Novel Treatment for Plantar Fasciitis, *J Foot Ankle Surg* 2012, in press:
20. Guo L, Kubat NJ, Nelson TR, Isenberg RA: Meta-analysis of clinical efficacy of pulsed radio frequency energy treatment, *Ann Surg* 2012, 255:457-467
21. Eming SA, Krieg T, Davidson JM: Inflammation in wound repair: molecular and cellular mechanisms, *J Invest Dermatol* 2007, 127:514-525

22. Moffett J, Griffin NE, Ritz MC, George FR: Pulsed radio frequency energy field treatment of cells in culture results in increased expression of genes involved in the inflammation phase of lower extremity diabetic wound healing., *The Journal of Diabetic Foot Complications* 2010, 2:57-64
23. Moffett J, Kabut NJ, Griffin NE, Ritz MC, George FR: Pulsed radio frequency energy field treatment of cells in culture: Increased expression of genes involved in angiogenesis and tissue remodeling during wound healing., *The Journal of Diabetic Foot Complications* 2011, 3:30-39
24. Tepper OM, Callaghan MJ, Chang EI, Galiano RD, Bhatt KA, Baharestani S, Gan J, Simon B, Hopper RA, Levine JP, Gurtner GC: Electromagnetic fields increase in vitro and in vivo angiogenesis through endothelial release of FGF-2, *Faseb J* 2004, 18:1231-1233
25. Callaghan MJ, Chang EI, Seiser N, Aarabi S, Ghali S, Kinnucan ER, Simon BJ, Gurtner GC: Pulsed electromagnetic fields accelerate normal and diabetic wound healing by increasing endogenous FGF-2 release, *Plast Reconstr Surg* 2008, 121:130-141
26. Woo KY: Wound-related pain: anxiety, stress and wound healing, *Wounds UK* 2010, 6:92-98
27. McGuire L, Heffner K, Glaser R, Needleman B, Malarkey W, Dickinson S, Lemeshow S, Cook C, Muscarella P, Melvin WS, Ellison EC, Kiecolt-Glaser JK: Pain and wound healing in surgical patients, *Ann Behav Med* 2006, 31:165-172
28. Maier M: Pulsed radio frequency energy in the treatment of painful chronic cutaneous wounds: a report of two cases, *Pain Med* 2011, 12:829-832
29. Stiller MJ, Pak GH, Shupack JL, Thaler S, Kenny C, Jondreau L: A portable pulsed electromagnetic field (PEMF) device to enhance healing of recalcitrant venous ulcers: a double-blind, placebo-controlled clinical trial, *Br J Dermatol* 1992, 127:147-154
30. Tung S, Khaski A, Milano E, Kay C: The application of Diapulse in the treatment of decubitus ulcers: case reports, *Contemp Surg* 1995, 47:27-32



Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

Original Research

Pulsed Radiofrequency Electromagnetic Field Therapy: A Potential Novel Treatment of Plantar Fasciitis

Joel Brook, DPM, FACFAS¹, Damien M. Dauphinee, DPM, FACFAS², Jaryl Korpinen, DPM, FACFAS³, Ian M. Rawe, PhD⁴¹ Dallas Podiatry Works, Dallas, TX; and Education Director, Podiatric Surgery Residency Program, Hunts Regional Medical Center, Greenville, TX² Complete Foot and Ankle Care of North Texas, PA, Denton, TX³ Premier Foot and Ankle, Plano, TX⁴ Director, Clinical Research, BioElectronics Corp, Frederick, MD

ARTICLE INFO

Level of Clinical Evidence: 1

Keywords:

calcaneus

heel

medication

pain

quality of life

ABSTRACT

Plantar fasciitis is a common cause of heel pain, and although treatments are usually conservative, they can take up to 2 years to achieve resolution. A double-blind, multicenter, randomized, placebo-controlled study was used to evaluate a small, wearable, extended-use pulsed radiofrequency electromagnetic field (PRFE) device as a treatment of plantar fasciitis. A total of 70 subjects diagnosed with plantar fasciitis were enrolled in the present study. The subjects were randomly assigned a placebo or active PRFE device. The subjects were instructed to wear the PRFE device overnight, record their morning and evening pain using a 0- to 10-point visual analog scale (VAS), and log any medication use. The primary outcome measure for the present study was morning pain, a hallmark of plantar fasciitis. The study group using the active PRFE device showed progressive decline in morning pain. The day 7 AM-VAS score was 40% lower than the day 1 AM-VAS score. The control group, in comparison, showed a 7% decline. A significantly different decline was demonstrated between the 2 groups ($p = .03$). The PM-VAS scores declined by 30% in the study group and 19% in the control group, although the difference was not significant. Medication use in the study group also showed a trend downward, but the use in the control group remained consistent with the day 1 levels. PRFE therapy worn on a nightly basis appears to offer a simple, drug-free, noninvasive therapy to reduce the pain associated with plantar fasciitis.

© 2012 by the American College of Foot and Ankle Surgeons. All rights reserved.

The plantar fascia is a thick fibrous band of connective tissue originating on the bottom surface of the calcaneus (heel bone) and extending along the sole of the foot toward the 5 toes. It acts to support the arch of the foot and aids in resupination of the foot during propulsion (1). The condition "plantar fasciitis" is the most common cause of heel pain, and estimates indicate that 1 million physician visits annually involve the diagnosis and treatment of plantar fasciitis (2). In addition, it is a common complaint in athletes, resulting in approximately 8% of all running-related injuries (3,4).

The pain from plantar fasciitis is usually felt in the heel of the foot and is usually most acute during the first steps in the morning because the fascia tightens up during the night during sleep. As the tissue warms, the pain subsides but can return with activity and long periods of standing. The underlying condition is a degenerative

condition, caused by microscopic tears in the collagen of the fascia. The condition has a detrimental effect on the quality of life, and although conservative treatments are often effective, the period to resolution can be up to 2 years. However, most patients experience improvement by 9 months (5). Conservative therapies include rest, nonsteroidal anti-inflammatory medication, night splints, foot orthotics (6), and stretching protocols (7) of the plantar fascia and gastrocnemius/soleus muscle (8). For persistent plantar heel pain, extracorporeal shock wave therapy has been used but with mixed success. Surgery is sometimes used as a last resort but complications can arise, and it is not always successful (9).

Pulsed radiofrequency electromagnetic field (PRFE) therapy or pulsed electromagnetic field therapy has a long history in treating medical conditions. In 1947, the Federal Communications Commission assigned 3 frequencies at the short end of the radiofrequency band for medical use (40.68 MHz, 13.56 MHz, and 27.12 MHz) (10). The frequency of 27.12 MHz is the most widely used in clinical practice. The first PRFE device, the Diapulse (Daipulse, Great Neck, NY) was commercially available in the 1950s and was followed by other commercially available machines. PRFE is a noninvasive therapy that

Financial Disclosure: None reported.**Conflict of Interest:** I. Rawe is a paid employee of Bioelectronics Corp.

Address correspondence to: Ian M. Rawe, PhD, Director, Clinical Research, BioElectronics Corp, 4539 Metropolitan Court, Frederick, MD 21704.

E-mail address: irawe@bielcorp.com (I.M. Rawe).

delivers electromagnetic energy into soft tissue, generating an electric field that is thought to mediate the therapeutic effects (11). Many studies have shown the clinical efficacy and safety of PRFE therapy recently reviewed by Guo et al (12). For soft tissue injury, these include ankle inversion treatment, in which studies showed a reduction in pain and swelling (13,14). PRFE therapy has shown to be beneficial in the treatment of neck pain (10,15). The treatment of osteoarthritis with PRFE has been reported to improve joint mobility and decrease pain and stiffness (16–18). Recently, there has been a focus on PRFE therapy and its application in controlling postoperative pain and in promoting the healing of chronic wounds. Significant decreases in postoperative pain have been reported after breast augmentation (19,20) and breast reduction surgery (21), with a corresponding decreased need for narcotic pain medication during recovery. Healing of chronic wounds has also been reported in a number of case reports (22–26), and a retrospective study of a wound registry showed that PRFE holds promise to effectively promote the healing of chronic wounds (27). Significantly, studies on animal models of Achilles tendon repair showed increased tensile strength and collagen alignment (28,29) after PRFE treatment. At 3 weeks after transection of the rat Achilles tendon, the tensile strength had increased by 69% compared with the nontreated control rats (29). Also, in a model of Achilles tendonitis, increased collagen alignment, decreased inflammation, and better tissue normality was seen (28). In vitro cuts in primary human tenocyte cultures from supraspinatus and quadriceps tendons exposed to electromagnetic field stimulation showed significantly accelerated cut closure 12 and 24 hours after the injury (30).

Classically, most studies of PRFE have used large, fixed main-powered devices, in which therapy is delivered in the clinic. In the present exploratory study for the treatment of plantar fasciitis, we used an innovative, small, wearable PRFE device (ActiPatch, Bio-Electronics, Frederick, MD) that can be used for extended periods. In the present study, it was used as a home-based therapy delivered nightly during sleep.

Patients and Methods

The study was a multicenter, prospective, randomized, double-blind, and placebo- and positive-controlled trial to determine the effects of nightly use of a wearable PRFE device (ActiPatch, Bioelectronics). The North Texas institutional review board at Medical City Dallas approved the study, the study participants provided signed consent forms, and all rights of the enrolled subjects in the present study were protected. The primary outcome measure for the study was morning pain, selected because morning pain is the hallmark of plantar fasciitis. Subjects who had been diagnosed with plantar fasciitis were recruited from the clinical practices of the podiatrist authors. The primary diagnostic criteria was defined as the presence of tenderness at the insertion of the plantar fascia into the heel bone, either plantar medially or plantarly. Radiography was used in all cases to rule out osseous causes of heel pain, including stress fracture or bone tumor. Although patients with fat pad atrophy were not excluded, those with pain directly under the osseous prominence of the calcaneal tuber rather than at the insertion of the plantar fascia, were excluded. Patients in whom neuritis was found to be the primary cause of heel pain as determined by palpation or percussion of the branches of the medial and lateral calcaneal nerves were excluded. Each subject recruited into the study randomly selected a coded PRFE device. The device used in the present study was a pulsed radiofrequency energy device (ActiPatch) that 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 and a 100- μ s burst width. The peak burst output power of the 12-cm antenna is approximately 0.0098 W and covers a surface area of approximate 103 cm². The circuitry consists of low voltage (3 V) digital/analog electronics that control all timing functions to produce the therapeutic radiofrequency field, with the antenna field placed directly above the therapeutic site. This closed loop system of the antenna, low-energy signal generator circuit, and battery power supply transfers the radiofrequency energy to the tissue. The placebo devices did not emit a radiofrequency electromagnetic field but were identical to the active devices, including a light-emitting diode (LED) light showing operation. The energy from the active device is not felt by the user, and the active device cannot be distinguished in any way from the placebo device. Subjects were trained in the use of the PRFE device, which was worn nightly for 7 days with the antenna placed over the heel, the site of pain. The device was kept in place

with a wrap and switched off when not in use. No other new treatments were started during the study period.

The subjects were asked to record their pain levels using a 0 to 10 visual analog scale (VAS). The VAS scores were recorded in the morning (AM), assessed on the first steps after awakening, and at night (PM), before bed, for the 7 days of the study. Medication use was also recorded, and medication use was left to the discretion of the patients during the study period.

Statistical Analysis

After completion of the study period and the collection of all available data, the data were analyzed using Excel 2007 (Yuma, AZ) with QI macros (KnowWare International, Denver, CO). Analysis of variance was performed using a generalized linear model, a flexible generalization of ordinary linear regression using SAS software (SAS Institute, Cary, NC). The generalized linear model generalizes linear regression by allowing the linear model to be related to the response variable by way of a link function and by allowing the magnitude of the variance of each measurement to be a function of its predicted value. The slope or rate of decline was compared using repeated measure analysis, which allows for the comparison of the mean variables with time. This analysis allows for a statistical comparison between the rate of decline in the control and study groups. The slope is considered significantly different at the 95% confidence level. Trends in VAS scores were analyzed using the Friedman test for nonparametric repeated measures. The base rates for each group were done relative to the first VAS score taken in the morning of day 1.

Although not typically used, to show the group trends in medication use during the 7-day study period, the following method was used. Medications were converted to 1 pill doses using a base dose for each medication used by the study participants. One pill was recoded as 200 mg ibuprofen, 250 mg acetaminophen, 250 mg naproxen, or 100 mg celecoxib. The use of a diclofenac topical patch was recorded as 1 dose.

Results

The planned enrollment for the study was 140 patients, and 70 active- and 70 placebo-coded devices were mixed in boxes. The patients randomly chose a device, and the device code was recorded. The planned enrollment was not met owing to time constraints, and only 70 patients were enrolled in the study (42 active and 28 placebo). Given the shortness of the study period and the simplicity of the treatment, no patients were lost to follow-up and no data were missing. Although this was a multicenter study, an intersite analysis was not performed because subject site recruitment data were not recorded by the study coordinator.

The demographic data indicated the randomization was successful (Table 1). No significant difference was found in age, height, weight, or plantar fasciitis duration between the 2 groups. The percentage of females in the 2 groups was 75% in the control group and 73.8% in the study group.

The PRFE therapy devices were well tolerated by all the patients, and no adverse effects were noted. Data were obtained from all 70 enrolled patients and were available for statistical analysis. The mean AM-VAS scores and the standard deviation for the 7 days of the study are presented in Table 2.

The day 1 VAS scores were not significantly different between the study and control groups. The VAS pain scores for the 7 days of the study showed a consistency in the control group with a day 1 to day 7 difference of 0.26 VAS points. In contrast, the AM-VAS score in the study group showed a steady decline. The day 1 to day 7 VAS score difference was 1.74 VAS points, for a 7.5-fold greater reduction in pain than in the control group (Fig. 1). Regression analysis of the

Table 1
Demographic data (N = 70 patients)

Variable	Control Group (n = 28 patients)	Study Group (n = 42 patients)	p Value
Age (y)	49.7 $\pm$ 15.2	53.2 $\pm$ 14.7	.35
Height (in.)	64.3 $\pm$ 2.9	65.5 $\pm$ 3.0	.09
Weight (lb)	196.4 $\pm$ 58.6	176.0 $\pm$ 28.8	.14
Plantar fasciitis duration (mo)	13.1 $\pm$ 8.7	11.9 $\pm$ 8.1	.60

Data presented as mean $\pm$ standard deviation, with no significant difference ($p \leq .05$) detected between the 2 groups.

Table 2
Mean morning visual analog scale scores (N = 70 patients)

Day	AM-VAS Score	
	Control Group (n = 28 patients)	Study Group (n = 42 patients)
1	3.67 ± 2.01	4.38 ± 2.39
2	3.75 ± 2.30	3.64 ± 2.15
3	3.28 ± 2.40	3.45 ± 2.11
4	3.13 ± 2.37	3.26 ± 1.91
5	3.54 ± 2.86	2.87 ± 2.16
6	3.30 ± 2.59	3.01 ± 2.13
7	3.41 ± 2.80	2.64 ± 1.88

Abbreviation: AM-VAS, morning visual analog scale.

Data presented as mean ± standard deviations.

Friedman test for nonparametric repeated measures showed significant difference ($p = .036$) between mean values for control and study groups.

study group showed an R^2 of 0.887 ($p = .002$, slope = -0.252 ; i.e., $y = 4.33 - 0.252 \times \text{day}$). For the control group, the R^2 was 0.239 ($p = .265$, slope = -0.051 ; i.e., $y = 3.643 - 0.051 \times \text{day}$). The regression analysis showed a significant downward slope of 0.25 VAS points/day in the study group. A standard repeated measure analysis using the SAS generalized linear model routine showed significantly different rates of improvement in morning pain between the 2 groups ($p = .03$). An F test was also performed using Excel 2007 QI macros and showed the group means to be significantly different ($p = .036$).

The AM-VAS scores from day 2 through day 7 were compared with the day 1 AM-VAS scores using the Student's t test (Table 3). The AM-VAS scores from day 2 to day 7 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 had become significantly different at day 4 ($p = .021$) compared with the day 1 score. The decline in pain continued to be significant through day 7.

The mean PM-VAS score with standard deviation is listed in Table 4. The control and study groups showed declines compared with the day 1 VAS scores.

The decline in the control group was 1.05 VAS points or 19%, and the decline in the study group was 1.49 VAS points or 30%. The SAS analysis of variance and F test showed no significant difference between the 2 groups. However, the decline in the control group from day 1 to day 2 was 0.64 VAS point and an additional 0.36 VAS point from day 2 to day 3. From day 3 to day 7, no additional decline occurred in the mean VAS score (4.46 and 4.41 points, respectively). In contrast, the VAS score decline was more evenly spread in the study group, with a day 1 to day 2 decline of 0.33 VAS point and a day 2 to day 3 decline of 0.39 point. The VAS point decline from day 3 to day 7 was 0.77 VAS point in the study group. Fig. 2A shows the mean decline in the PM-VAS score for both groups during the 7-day study period, and Fig. 2B shows the day 3 to 7 mean decline.

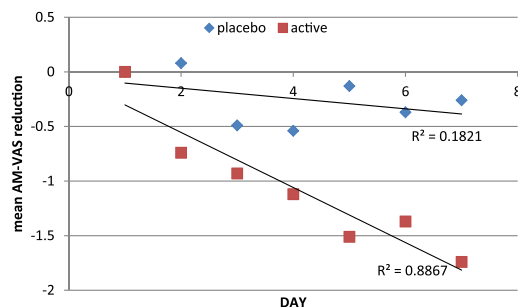


Fig. 1. Effect of overnight use of ActiPatch device on morning pain. Data presented as mean reduction in morning visual analog scale (AM-VAS) score for pain from day 1 to day 7. As can be clearly seen, the level of pain decrease in the treated group was greater than that of the control group by a factor of 7.5.

Table 3
AM-VAS scores on day 2 through day 7 compared with day 1 score using Student's t test (N = 70 patients)

Day	p Value	
	Control Group (n = 28 patients)	Study Group (n = 42 patients)
2	.90	.15
3	.52	.06
4	.36	.021*
5	.83	.0035*
6	.61	.0076*
7	.69	.00045*

Abbreviation: AM-VAS, morning visual analog scale.

* Statistically significant difference.

The results of the PM-VAS analysis were similar to those of AM-VAS analysis, when comparing the scores of day 2 through day 7 with the day 1 scores using the Student's t test. Significance was shown for days 4 through 7 in the study group, with no significant decrease seen in the control group (Table 5).

Medication

The medication used by each group is shown in Table 6. Although the randomization of the study was successful as shown by the demographic data (Table 1), a greater percentage of patients were taking medication in the control group (9/28, 32.1%) compared with the study group (10/42, 23.8%) on day 1. However, of those patients in the 2 study groups taking medication, the average pill use on day 1 was very similar (control group, 2.55; study group, 2.44 pills per subject; Table 7). This was also shown by the total pill use, which was similar at day 1 (study group, 22; control group, 23). The daily total pill use and average patient pill use in the control group showed day to day variability but showed no decline overall. In contrast, in the study group, the total pill and patient average use showed a downward trend (Table 7 and Fig. 3). By day 7, the pill use in the control group was 28 and in the study group was 11, and the average pill use was 2.8 pills per patient in the control group and 1.57 pills per patient in the study group. The number of patients taking pills in the control group was 10 (35.7%) of 28 and in the study group was 7 (16.6%) of 42 at day 7. However, no significant difference was found between the 2 groups.

Discussion

In the present study, we have presented the results from a prospective study using a small, lightweight wearable PRFE device as a treatment for plantar fasciitis. The subjects were instructed to wear the device overnight and the pain experienced in the morning and evening was recorded for 7 days. The results showed that overnight wear of the PRFE device was effective at significantly reducing morning pain, a hallmark of plantar fasciitis. The significant decline in

Table 4
Mean daily PM-VAS scores

Day	Control Group		Study Group	
	Mean Score	Day to Day Decline	Mean Score	Day to Day Decline
1	5.46 ± 2.7	—	4.97 ± 2.5	—
2	4.82 ± 2.9	−0.64	4.64 ± 2.5	−0.33
3	4.46 ± 2.9	−0.36	4.25 ± 2.7	−0.39
4	4.59 ± 3.1	+0.13	3.74 ± 2.2	−0.51
5	4.45 ± 3.0	−0.14	3.81 ± 2.4	+0.06
6	4.14 ± 2.8	−0.31	3.79 ± 2.5	−0.02
7	4.41 ± 2.9	+0.33	3.48 ± 2.4	−0.31
Total	—	−1.05	—	−1.49

Abbreviation: PM-VAS, evening visual analog scale.

Data presented as mean ± standard deviation.

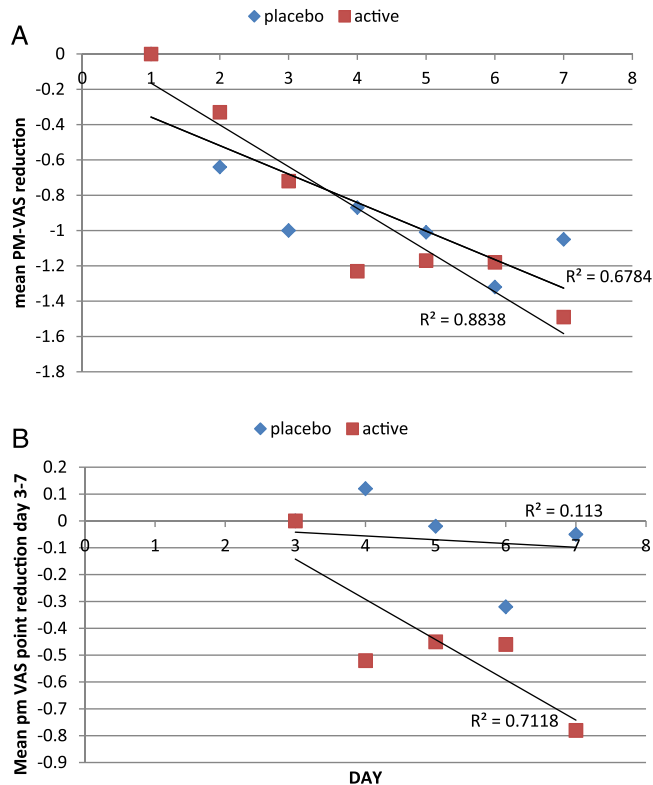


Fig. 2. (A) Mean evening visual analog scale (PM-VAS) point reduction after overnight use of Actipatch device. Data are presented as mean reduction in evening visual analog scale pain from day 1 to day 7, with no significant difference between the 2 groups. The study group decreased 1.49 visual analog scale points compared with 1.05 visual analog scale points in the control group. (B) Mean evening visual analog scale score reduction from days 3 to 7. Data show that the control group mean evening visual analog scale score remained essentially unchanged from day 3 through day 7 but study group mean evening visual analog scale score showed a continued decline.

morning pain in the study group wearing the active PRFE device was 40% compared with the 7.9% in the control group during the 7-day study period. The analysis of the nighttime pain showed no significant difference between the 2 groups. The pain declined 30% in the study group and 19% in the control group. The control group had a day 1 to day 3 decline of 1.00 VAS point in the evening, although very little decline (0.05 VAS points) was seen for the following 3 to 7 days. This suggests that there was a strong initial placebo effect for the first few days of the study. The decline in the study group was more consistent, indicating a longer study period would have resulted in a significance difference between the 2 groups. Medication use in the study group showed a downward trend during the 7-day study but remained more consistent in the control group, although the results were not significantly different. The consistent decreases in morning pain seen

Table 5

PM-VAS scores on day 2 through day 7 compared with day 1 score using Student's *t* test (n = 70 patients)

Day	p Value	
		Control Group (n = 28 patients)
		Study Group (n = 42 patients)
2	.41	.55
3	.20	.21
4	.28	.02*
5	.20	.03*
6	.08	.03*
7	.17	.007*

Abbreviation: PM-VAS, evening visual analog scale.

* Statistically significant.

Table 6

Group medication use (N = 70 patients)

Medication	Control Group (n)	Study Group (n)
Acetaminophen 250 mg	3	24
Ibuprofen 200 mg	85	46
Naproxen 250 mg	38	22
Celebrex	28	0
Flector patch (diclofenac)	0	7
Loratab	0	2
Total	154	101

Control group used 154 pain medication pills compared with 101 pain medication pills in the study group. (1 pill counted as 200 mg ibuprofen, 250 mg acetaminophen, 250 mg naproxen, 100 mg celebrex, or 1 Flector patch).

in the study group would be expected to lead to decreased medication use, which occurred.

The PRFE device used in the present study is based on work pioneered by Bental (31) in the 1980s who first showed that reducing the power and size but extending the use time produced equivalent results to larger, more powerful devices. A study by Nicolle and Bental (32) on surgical recovery showed that extended-use PRFE devices were able to control edema after blephoroplasty. There has been a new focus on small, extended-use PRFE devices, and a number of studies on post-operative recovery and wound healing have been published (19–21,26).

The current treatment for most plantar fasciitis cases results in positive resolution with conservative modalities (6,33–36). Conservative forms of treatment, including nonsteroidal anti-inflammatory drugs, heel pads or orthotics, physical therapy, stretching of the gastrocnemius-soleus, and corticosteroid injections, provide substantial relief for about 80% of patients. However, along with the long interval to resolution, these treatments have additional drawbacks. Injection of corticosteroids for the treatment of plantar fasciitis is almost always painful and can cause both local and systemic side effects (37). Long-term use of nonsteroidal anti-inflammatory drugs can have significant side effects such as gastrointestinal complications and an increased risk of serious cardiovascular events (38). Although custom orthotics are often prescribed, they may only show a short-term benefit in reducing the pain associated with plantar fasciitis (39).

After failure of conservative therapy, treatments such as extracorporeal shock wave therapy and surgery, are used. Extracorporeal shock wave therapy has been reported to be effective in some studies after conservative treatment has failed. Metzner et al (40) reported good results with extracorporeal shockwave therapy. In their study, success was defined as a 30% VAS reduction, which was seen in 81% of patients at 6-week follow-up. However, other studies have reported conflicting results, with the treatment seeming no better than sham therapy (41–43). Although surgery to treat plantar fasciitis is used as a last resort, it has had a variable (70–90%) success rate, and recovery from surgery can vary from several weeks to a few months. Potential complications include transient swelling of the heel, heel hypoesthesia, rupture of plantar fascia, flattening of the longitudinal arch, and calcaneal fracture (9).

Table 7

Medication use (N = 70 patients)

Variable	Day						
	1	2	3	4	5	6	7
Control group (n = 28 patients)							
Subjects using medication	9	8	10	8	9	8	10
Total medication use	23	21	24	19	20	19	28
Average pill use	2.55	2.65	2.4	2.37	2.22	2.37	2.80
Study group (n = 42 patients)							
Subjects using medication	9	7	7	5	7	8	7
Total medication use	22	16	12	7	17	16	11
Average pill use	2.44	2.28	1.71	1.4	2.42	2.0	1.57

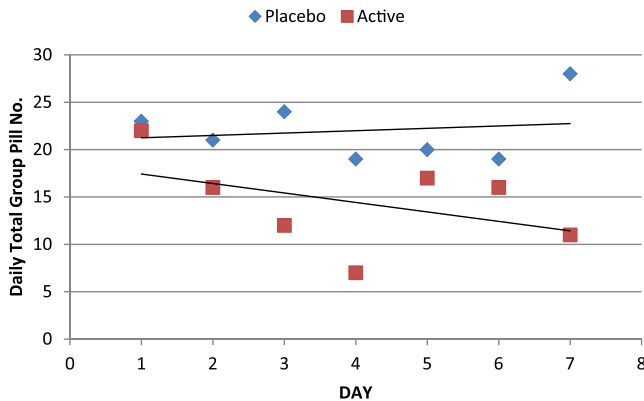


Fig. 3. Mean daily pill use for study and control groups showing decline in pill use in the study group from 22 pills on day 1 to 11 pills on day 7. In contrast, no decline in pill use was seen in the control group (23 pills on day 1 and 28 pills on day 7).

This is the first study to show that PRFE therapy used in this format can potentially treat plantar fasciitis. PRFE therapy for plantar fasciitis appears to offer a therapy that is easy to use, noninvasive, and drug free, with no reported side effects. The results from the present initial study indicate that PRFE therapy results in a relatively rapid decline of pain, given the usually protracted nature of the condition. However, the present study had a number of limitations, including the length of time that data was collected (7 days), the lack of long-term follow-up, and the lack of intercenter analysis. Also, no power analysis was performed to calculate the study size, owing to the lack of data on the effects of this form of therapy on plantar fasciitis heel pain. The sample size was determined by the amount of time the podiatric authors could allot to do the study, which resulted in lower than anticipated recruitment goals. However, the study results suggest that PRFE therapy in this form holds promise as a new treatment of plantar fasciitis.

This is the first study using this form of therapy for plantar fasciitis heel pain. The results from our study indicate that additional studies are warranted to confirm these initial findings.

References

- Michaud TC. *Foot Orthoses and Other Forms of Conservative Foot Care*. Lippincott, Williams & Wilkins, Massachusetts, 1997.
- Riddle DL, Schappert SM. Volume of ambulatory care visits and patterns of care for patients diagnosed with plantar fasciitis: a national study of medical doctors. *Foot Ankle Int* 25:303–310, 2004.
- Taunton JE, Ryan MB, Clement DB, McKenzie DC, Lloyd-Smith DR, Zumbo BD. A retrospective case-control analysis of 2002 running injuries. *Br J Sports Med* 36:95–101, 2002.
- Lysholm J, Wiklander J. Injuries in runners. *Am J Sports Med* 15:168–171, 1987.
- Urovitz EP, Birk-Urovitz A, Birk-Urovitz E. Endoscopic plantar fasciotomy in the treatment of chronic heel pain. *Can J Surg* 51:281–283, 2008.
- Lynch DM, Goforth WP, Martin JE, Odom RD, Preece CK, Kotter MW. Conservative treatment of plantar fasciitis: a prospective study. *J Am Podiatr Med Assoc* 88:375–380, 1998.
- Glazer JL. An approach to the diagnosis and treatment of plantar fasciitis. *Phys Sports Med* 37:74–79, 2009.
- Barry LD, Barry AN, Chen Y. A retrospective study of standing gastrocnemius-soleus stretching versus night splinting in the treatment of plantar fasciitis. *J Foot Ankle Surg* 41:221–227, 2002.
- Young CC, Rutherford DS, Niedfeldt MW. Treatment of plantar fasciitis. *Am Fam Physician* 63:467–474, 477–478, 2001.
- Foley-Nolan D, Barry C, Coughlan RJ, O'Connor P, Roden D. Pulsed high frequency (27 MHz) electromagnetic therapy for persistent neck pain: a double blind, placebo-controlled study of 20 patients. *Orthopedics* 13:445–451, 1990.
- Kloth LC, Pilla AA. Electromagnetic stimulation for wound repair. In: *Wound Healing: Evidence-Based Management*, FA Davis, Philadelphia, 2010, pp. 514–544.
- Guo L, Kubat NJ, Isenberg RA. Pulsed radio frequency energy (PRFE) use in human medical applications. *Electromagn Biol Med* 30:21–45, 2011.
- Pennington GM, Danley DL, Sumko MH, Bucknell A, Nelson JH. Pulsed, non-thermal, high-frequency electromagnetic energy (DIAPULSE) in the treatment of grade I and grade II ankle sprains. *Mil Med* 158:101–104, 1993.
- Wilson DH. Comparison of short wave diathermy and pulsed electromagnetic energy in treatment of soft tissue injuries. *Physiotherapy* 60:309–310, 1974.
- Foley-Nolan D, Moore K, Codd M, Barry C, O'Connor P, Coughlan RJ. Low energy high frequency pulsed electromagnetic therapy for acute whiplash injuries: a double blind randomized controlled study. *Scand J Rehabil Med* 24:51–59, 1992.
- Laufer Y, Zilberman R, Porat R, Nahir AM. Effect of pulsed short-wave diathermy on pain and function of subjects with osteoarthritis of the knee: a placebo-controlled double-blind clinical trial. *Clin Rehabil* 19:255–263, 2005.
- Jan MH, Chai HM, Wang CL, Lin YF, Tsai LY. Effects of repetitive shortwave diathermy for reducing synovitis in patients with knee osteoarthritis: an ultrasonographic study. *Phys Ther* 86:236–244, 2006.
- Callaghan MJ, Whittaker PE, Grimes S, Smith L. An evaluation of pulsed shortwave diathermy for reducing synovitis using radioleucoscintigraphy: a randomised, double blind, controlled trial. *Joint Bone Spine* 72:150–155, 2005.
- Rawe IM, Lowenstein A, Barcelo CR, Genecov DG. Control of postoperative pain with a wearable continuously operating pulsed radio frequency energy device—a preliminary study. *Aesthetic Plast Surg Epub*, 2011 Oct 25.
- Heden P, Pilla AA. Effects of pulsed electromagnetic fields on postoperative pain: a double-blind randomized pilot study in breast augmentation patients. *Aesthetic Plast Surg* 32:660–666, 2008.
- Rohde C, Chiang A, Adipoju O, Casper D, Pilla AA. Effects of pulsed electromagnetic fields on interleukin-1 beta and postoperative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients. *Plast Reconstr Surg* 125:1620–1629, 2010.
- Fletcher S. Successful treatment of venous stasis ulcers with combination compression therapy and pulsed radio frequency energy in a patient scheduled for amputation. *J Wound Ostomy Continence Nurs* 38:91–94, 2011.
- Frykberg R, Martin E, Tallis A, Tierney E. A case history of multimodal therapy in healing a complicated diabetic foot wound: negative pressure, dermal replacement and pulsed radiofrequency energy therapies. *Int Wound J* 8:132–139, 2011.
- Larsen JA, Overstreet J. Pulsed radiofrequency energy in the treatment of complex diabetic foot wounds: two cases. *J Wound Ostomy Continence Nurs* 35:523–527, 2008.
- Maier C, Kibbel K, Mercker S, Wulf H. [Postoperative pain therapy at general nursing stations: an analysis of eight years' experience at an anesthesiological acute pain service]. *Anaesthesist* 43:385–397, 1994.
- Rawe IM, Vlahovic TC. The use of a portable, wearable form of pulsed radio frequency electromagnetic energy device for the healing of recalcitrant ulcers: a case report. *Int Wound J Epub* 2011 Sept 20.
- Frykberg RG, Driver VR, Lavery LA, Armstrong DG, Isenberg RA. The use of pulsed radiofrequency energy therapy in treating lower extremity wounds: results of a retrospective study of a wound registry. *Ostomy Wound Manage* 57:22–29, 2011.
- Lee EW, Maffulli N, Li CK, Chan KM. Pulsed magnetic and electromagnetic fields in experimental Achilles tendonitis in the rat: a prospective randomized study. *Arch Phys Med Rehabil* 78:399–404, 1997.
- Strauch B, Patel MK, Rosen DJ, Mahadevia S, Brindzei N, Pilla AA. Pulsed magnetic field therapy increases tensile strength in a rat Achilles' tendon repair model. *J Hand Surg Am* 31:1131–1135, 2006.
- Denaro V, Ruzzini L, Barnaba SA, Longo UG, Campi S, Maffulli N, Sgambato A. Effect of pulsed electromagnetic fields on human tenocyte cultures from supraspinatus and quadriceps tendons. *Am J Phys Med Rehabil* 90:119–127, 2011.
- Bentall RHC. Low-level pulsed radiofrequency fields and the treatment of soft-tissue injuries. *Bioelectrochem Bioenerg* 16:531–548, 1986.
- Nicoll FV, Bentall RM. Use of radio-frequency pulsed energy in the control of postoperative reaction in blepharoplasty. *Aesthetic Plast Surg* 6:169–171, 1982.
- DiGiovanni BF, Nawoczenski DA, Lintal ME, Moore EA, Murray JC, Wilding GE, Baumhauer JF. Tissue-specific plantar fascia-stretching exercise enhances outcomes in patients with chronic heel pain: a prospective, randomized study. *J Bone Joint Surg Am* 85-A:1270–1277, 2003.
- Pfeffer G, Bacchetti P, Deland J, Lewis A, Anderson R, Davis W, Alvarez R, Brodsky J, Cooper P, Frey C, Herrick R, Myerson M, Sammarco J, Janecki C, Ross S, Bowman M, Smith R. Comparison of custom and prefabricated orthoses in the initial treatment of proximal plantar fasciitis. *Foot Ankle Int* 20:214–221, 1999.
- Buchbinder R. Clinical practice: plantar fasciitis. *N Engl J Med* 350:2159–2166, 2004.
- Landorf KB, Keenan AM, Herbert RD. Effectiveness of different types of foot orthoses for the treatment of plantar fasciitis. *J Am Podiatr Med Assoc* 94:542–549, 2004.
- Brinks A, Koes BW, Volkers AC, Verhaar JA, Bierma-Zeinstra SM. Adverse effects of extra-articular corticosteroid injections: a systematic review. *BMC Musculoskelet Disord* 11:206, 2010.
- Peterson K, McDonagh M, Thakurta S, Dana T, Roberts C, Chou R, Helfand M. In Drug Class Review: Nonsteroidal Anti-inflammatory Drugs (NSAIDs). Final Update 4 Report, Portland, OR, 2010.
- Landorf KB, Keenan AM, Herbert RD. Effectiveness of foot orthoses to treat plantar fasciitis: a randomized trial. *Arch Intern Med* 166:1305–1310, 2006.
- Metzner G, Dohnalek C, Aigner E. High-energy extracorporeal shock-wave therapy (ESWT) for the treatment of chronic plantar fasciitis. *Foot Ankle Int* 31:790–796, 2010.
- Haake M, Buch M, Schoellner C, Goebel F, Vogel M, Mueller I, Hausdorf J, Zamzow K, Schade-Brittinger C, Mueller HH. Extracorporeal shock wave therapy for plantar fasciitis: randomised controlled multicentre trial. *BMJ* 327:75, 2003.
- Speed CA, Nichols D, Wies J, Humphreys H, Richards C, Burnet S, Hazleman BL. Extracorporeal shock wave therapy for plantar fasciitis: a double blind randomised controlled trial. *J Orthop Res* 21:937–940, 2003.
- Buchbinder R, Ptasznik R, Gordon J, Buchanan J, Prabakaran V, Forbes A. Ultrasound-guided extracorporeal shock wave therapy for plantar fasciitis: a randomized controlled trial. *JAMA* 288:1364–1372, 2002.

Differentiation of Osteoprogenitor Cells Is Induced by High-Frequency Pulsed Electromagnetic Fields

Chad M. Teven, BS,* Matthew Greives, MD,* Ryan B. Natale, MS,* Yuxi Su, MD,†
Qing Luo, MD, PhD,† Bai-Cheng He, MD,† Deana Shenaq, MD,* Tong-Chuan He, MD, PhD,†
and Russell R. Reid, MD, PhD*

Abstract: Craniofacial defect repair is often limited by a finite supply of available autologous tissue (ie, bone) and less than ideal alternatives. Therefore, other methods to produce bony healing must be explored. Several studies have demonstrated that low-frequency pulsed electromagnetic field (PEMF) stimulation (ie, 5–30 Hz) of osteoblasts enhances bone formation. The current study was designed to investigate whether a Food and Drug Administration–approved, high-frequency PEMF–emitting device is capable of inducing osteogenic differentiation of osteoprogenitor cells. Osteoprogenitor cells (commercially available C3H10T1/2 and mouse calvarial) in complete Dulbecco modified Eagle medium were continuously exposed to PEMF stimulation delivered by the ActiPatch at a frequency of 27.1 MHz. Markers of cellular proliferation and early, intermediate, and terminal osteogenic differentiation were measured and compared with unstimulated controls. All experiments were performed in triplicate. High-frequency PEMF stimulation increases alkaline phosphatase activity in both cell lines. In addition, high-frequency PEMF stimulation augments osteopontin and osteocalcin expression as well as mineral nodule formation in C3H10T1/2 cells, indicating late and terminal osteogenic differentiation, respectively. Cellular proliferation, however, was unaffected by high-frequency PEMF stimulation. Mechanistically, high-frequency PEMF-stimulated osteogenic differentiation is associated with elevated mRNA expression levels of osteogenic bone morphogenetic proteins in C3H10T1/2 cells. Our findings suggest that high-frequency PEMF stimulation of osteoprogenitor cells may be explored as an effective tissue en-

gineering strategy to treat critical-size osseous defects of the craniofacial and axial skeleton.

Key Words: High-frequency pulsed electromagnetic fields; osteogenic differentiation; osteoprogenitor cell differentiation; pulsed electromagnetic fields

Abbreviations: ALP, alkaline phosphatase; BMP, bone morphogenetic protein; ERK-1, extracellular signal-regulated kinase 1; iCALs, immortalized calvarial cells; IHC, immunohistochemical; MAP, mitogen-activated protein; MSC, mesenchymal stem cell; OCN, osteocalcin; OPN, osteopontin; p38 α , p38-reactivating kinase; PBS, phosphate-buffered saline; PEMF, pulsed electromagnetic field

(*J Craniofac Surg* 2012;23: 586–593)

A major limitation in the repair of craniofacial defects lies in the finite supply of autologous tissue (ie, bone) available. Alternatives, such as demineralized bone matrix,¹ bone ceramics,² titanium,^{3,4} and porous polyethylene implants,⁵ are associated with an increased risk of infection, do not expand with a growing craniofacial skeleton (in the case of children), and can fail over time. In keeping with one of the core principles in tissue reconstruction, it is desirable to replace “like with like.” To this end, engineering of bone via cells capable of expansion and differentiation into bone is a valid strategy.

Many methods have been used to engineer bony tissue. For example, a useful and effective option is the transduction of target cells with an osteoinductive cytokine such as bone morphogenetic protein (BMP).^{6,7} However, this strategy is costly and can be confounded by infection risk, poor expression of the gene of interest, and the inability to modulate the gene of interest once the desired effect is achieved. An alternative approach, which avoids direct genetic alteration of target cells, is that of biophysical stimulation. Biophysical stimulation consisting of low-frequency pulsed electromagnetic fields (PEMFs) has been used clinically as adjunct treatment for processes affecting the musculoskeletal system for many years.^{8–14} At the cellular level, low-frequency PEMF stimulation is thought to modulate the expression level of endogenous osteogenic cytokines and their receptors.^{15–18} Nevertheless, the specific molecular mechanisms underlying the cellular response to PEMF stimulation have remained elusive.

Two key features of studies examining the osteoinductive effect of PEMFs are cell type and stimulation frequency. To this point, most scientists have evaluated the effect of PEMF stimulation on terminally differentiated osteoblasts. However, in situ cell populations at areas of bone growth are heterogeneous and contain cells at different stages of maturation. We therefore elected to investigate

From the *Laboratory of Craniofacial Biology & Development, Section of Plastic and Reconstructive Surgery, and †Molecular Oncology Laboratory, Department of Surgery, The University of Chicago Medical Center, Chicago, Illinois.

Received September 19, 2011.

Accepted for publication December 3, 2011.

Address correspondence and reprint requests to Dr Russell R. Reid, Section of Plastic and Reconstructive Surgery, University of Chicago Medical Center, 5841 S Maryland Ave MC 6035, Chicago, IL 60637; E-mail: rreid@surgery.bsd.uchicago.edu

The reported work was supported, in part, by research grants from the Pritzker School of Medicine (to C.M.T.), the American Cancer Society (T.-C.H.), the Brinson Foundation (T.-C.H.), the National Institutes of Health (T.-C.H. and R.R.R.), and the ASMS/Maxillofacial Surgeons Foundation (R.R.R.).

This study was presented at the Sixth Congress of the World Society for Reconstructive Microsurgery, Helsinki, Finland, 2011, and Selected for the 2011 ASMS Best Young Investigator Award.

The authors report no conflicts of interest.

Copyright © 2012 by Mutaz B. Habal, MD

ISSN: 1049-2275

DOI: 10.1097/SCS.0b013e31824cd6de

the effect of PEMFs on pluripotent cells. In addition, previous authors have generally exposed cells to low-frequency PEMF stimulation (ie, 5–30 Hz). A disadvantage of this subtype of PEMF stimulation is often the requirement for cofactors (eg, ascorbic acid, β -glycerophosphate, calcium phosphate [disks]) to induce differentiation *in vitro*.^{15,16} In contrast, the use of high-frequency PEMFs (ie, ≥ 1 MHz) to induce osteogenesis has not been previously described. Therefore, we examined whether high-frequency PEMF stimulation, like its low-frequency counterpart, has the ability to stimulate bone formation.

In the current study, osteoprogenitor cells were stimulated by a high-frequency PEMF-delivery device that is Food and Drug Administration (FDA) approved to treat soft tissue discomfort and edema in the postoperative setting.¹⁹ We show that this novel delivery system of high-frequency PEMFs is capable of augmenting osteogenic differentiation in murine progenitor cells without the aid of additional costimulants.

MATERIALS AND METHODS

Cell Culture and Chemicals

C3H10T1/2 cells were obtained from ATCC (Manassas, VA). Cells were maintained under conditions as described previously.^{20–22} Unless indicated otherwise, all chemicals were purchased from Sigma-Aldrich (St Louis, MO) or Fisher Scientific (Pittsburgh, PA). Of note, cells were cultured in medium that did not contain pro-osteogenic factors (eg, dexamethasone, ascorbic acid, β -glycerophosphate).

Immortalized calvarial cells (iCALs) were also used for experimentation. Briefly, calvariae were isolated from 3-week-old male CD-1 mice (Charles River, Wilmington, MA). Mice were housed in standard cages in an experimental animal room (24°C, 55% humidity, 1 atm, 12-hour light-dark cycle) and were fed a standard laboratory diet and water *ad libitum*. This investigation was approved by the Institutional Animal Care and Use Committee of the University of Chicago (Chicago, IL), and animal maintenance and experimental treatments were conducted in accordance with the ethical guidelines set forth by this committee. All procedures were conducted under sterile conditions.

Mice were killed, and calvariae were harvested by creating a midsagittal incision. The periosteum was incised to expose the calvarium on both sides of the midline. Soft tissue, dura, and remaining periosteum were removed. The isolated calvariae were washed repeatedly in phosphate-buffered saline (PBS) with 1% penicillin/streptomycin (p/s) solution, minced, and transferred to 10-mm² wells containing regular Dulbecco modified Eagle medium supplemented with 10% fetal bovine serum and 1% p/s solution (Sigma-Aldrich). Cultures were incubated at 37°C, 95% humidified air, and 5% CO₂. After approximately 7 days, cells grew to 80% confluency (percentage of cells covering the plate), at which point they were passaged by enzymatic digestion (0.1% trypsin; Sigma-Aldrich) to 25-cm² flasks containing 8 mL of Dulbecco modified Eagle medium with 10% fetal bovine serum and 1% p/s for experimentation. These cells display surface antigens found on mesenchymal stem cells (MSCs) and can differentiate into various mesenchymal tissues including bone and adipose (data not shown).

To allow for ease of culturing and preservation of cellular growth, harvested primary calvarial cells were allowed to grow in culture for 5 weeks and then underwent immortalization using a retroviral-mediated vector as previously described.²³ The immortalization process did not significantly alter the phenotype of this cell population (data not shown). Of note, early and late osteogenic differentiation and cellular proliferation of iCALs were examined, whereas all phases of differentiation (early, middle, and late) and proliferation of C3H10T1/2 cells were examined.

High-Frequency PEMF Stimulation

Pulsed electromagnetic fields were generated by the ActiPatch (BioElectronics, Frederick, MD). This device (Fig. 1A) has received FDA approval to treat soft tissue swelling, ecchymosis, and discomfort using low-energy, high-frequency PEMF technology. The nominal carrier frequency delivered is 27.1 MHz. The pulse frequency is 1000 Hz, with each pulse lasting 100 microseconds. The device produces an energy level of 50 to 100 μ V/cm up to a distance of 1 cm. A distance of 5 cm or greater from the PEMF-emitting region of the device effectively reduces this energy level to 0 μ V/cm. The device has a 720-hour battery life.

Unless otherwise indicated, stimulated cells were continuously exposed to PEMF stimulation (Fig. 1B). Untreated, control cells were kept at least 40 cm from the ActiPatch to ensure that they would not inadvertently be exposed to PEMF stimulation.

Alkaline Phosphatase Assay

Alkaline phosphatase (ALP) activity was assessed by a modified Great EscAPE SEAP Chemiluminescence Assay (BD Clontech, Mountain View, CA) as described previously.^{20,22,24–29} Both cell lines underwent ALP activity assays. Each assay condition was performed in triplicate, and the results were repeated in at least 3 independent experiments. The activity of the well-established early osteogenic marker ALP^{20,22,25–28} was measured on days 3, 5, 7, 9, and 12 of stimulation. Alkaline phosphatase activity was normalized by total cellular protein concentrations among the samples.

RNA Isolation and Semiquantitative Reverse Transcriptase–Polymerase Chain Reaction Analysis

Total RNA was isolated using TRIZOL Reagents (Invitrogen, Carlsbad, CA). Total RNA was used to generate cDNA templates by reverse transcriptase (RT) reaction with hexamer and Superscript II RT (Invitrogen). The first-strand cDNA products were further diluted 5- to 20-fold and used as polymerase chain reaction (PCR) templates. Semiquantitative RT-PCR was carried out as described previously.^{6,21,22,24,29–32} Polymerase chain reaction primers (Table 1) were designed using the Primer 3 program (Free Software Foundation, Inc, Boston, MA) to amplify the genes of interest (approximately 150–180 base pairs). A touchdown cycling program was as follows: 94°C for 2 minutes for 1 cycle, 92°C for 20 seconds, 68°C for 30 seconds, and 72°C for 12 cycles with a decrease in 1°C per cycle and then at 92°C for 20 seconds, 57°C for 30 seconds, and 72°C for seconds for 15 to 20 cycles, depending on the abundance of a given gene. The specificity of PCR products was confirmed by resolving PCR products on 1.0% agarose gels and visualized under a UV lamp and/or by ethidium bromide staining. All samples were normalized by the expression level of GAPDH. Reverse transcriptase–PCR data were analyzed by densitometry of gel bands

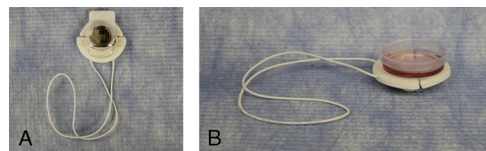


FIGURE 1. High-frequency PEMF delivery system. A, The ActiPatch is FDA approved for the treatment of soft tissue swelling, ecchymoses, and pain. This device was used as a novel delivery system of high-frequency PEMFs to evaluate the ability of high-frequency PEMF stimulation to induce osteogenic differentiation. The frequency of PEMF stimulation produced by this device is 27.1 MHz. B, Treated cells were exposed to continuous PEMF stimulation via placement on top of the PEMF-emitting region of the device for the duration of the experiment. Untreated, control cells were kept 40 cm or greater from the device, thereby precluding the possibility of PEMF stimulation.

TABLE 1. PCR Primers

Gene	Forward	Reverse
BMP-2	GCGTCAAGCCAAACACAA	CATGATAGCCCGGAGGTG
BMP-4	GCGAGCCATGCTAGTTTGA	AAGTGTCGCCTCGAAGTCC
BMP-6	GCAATCTGTGGGTGGTGAC	CTTGTCGTAAGGGCCGTCT
BMP-7	AGGAGCCAACAGACCAACC	TCACGTGCCAGAAGGAAAG
BMP-9	CGCAGCCTTAACCTCAGC	GTTGGAGGCAGGCGTAGA
ERK-1	CACGTTGGTACAGAGCTCCA	TGTGATTGAGCTGGTCAAGG
GAPDH	ACCCAGAAGACTGTGGATGG	CACATTGGGGGTAGGAACAC
OCN	CCTTCATGTCCAAGCAGGA	GGCGGTCTTCAAGCCATAC
p38 α	ACCCAGAAGACTGTGGATGG	CCCCATGAGATGGGTAC

using ImageJ software (<http://rsbweb.nih.gov/ij/download.html>) and normalized to GAPDH signals obtained from the same time point. The normalized data were expressed as relative changes in mRNA levels between PEMF-treated and untreated cells.

Immunohistochemical Staining

Immunohistochemical (IHC) staining was performed for osteopontin (OPN) and osteocalcin (OCN) as previously described.⁶ Cultured cells were either stimulated with high-frequency PEMFs or were left untreated. At day 10 of stimulation, cells were fixed with 10% formalin and washed with PBS. The fixed cells were permeabilized with 0.3% H₂O₂ and blocked with 10% goat serum, followed by incubation with an OPN or OCN antibody (both from Santa Cruz Biotechnology, Santa Cruz, CA) for 1 hour. After washing, cells were incubated with biotin-labeled secondary antibodies for 30 minutes, followed by incubating cells with streptavidin-horseradish peroxidase conjugate for 20 minutes at room temperature. The presence of the expected protein was visualized by 3,3'-diaminobenzidine staining and examined under a microscope. Stains without primary antibody were used as negative controls.

Matrix Mineralization Assay (Alizarin Red S Staining)

Cells (C3H10T1/2 and iCAL) were seeded in 24-well culture plates and were either PEMF stimulated or untreated. At day 14 of stimulation, mineralized matrix nodules were stained for calcium precipitation by means of alizarin red S staining, as described previously.⁶ Cells were fixed with 10% formalin at room temperature for 10 minutes. After being washed with PBS, fixed cells were incubated with 0.4% alizarin red S for 5 to 20 minutes, followed by extensive washing with PBS. The staining of calcium mineral deposits was recorded under bright-field microscopy.

Crystal Violet Viability Assay

Cellular proliferation was assessed by crystal violet staining. The crystal violet assay was conducted as described previously.^{33,34} Cells were plated in 6-well culture plates at a subconfluent condition ($\sim 10^5$ cells/well) and were treated with PEMF stimulation or control conditions. When cells from either group became 100% confluent, cells from both groups were carefully washed with PBS and stained with 0.5% crystal violet formalin solution at room temperature for 20 to 30 minutes. The stained cells were washed with tap water and air dried before macrographic images were taken.^{35,36} For quantitative measurement, the stained cells were dissolved in 10% acetic acid (2 mL per well for 6-well plate) at room temperature for 20 minutes with shaking. A 500- μ L portion was taken and added to 2 mL of double-distilled H₂O. Absorbance was measured at 570 to 590 nm.³⁷ Each assay condition was performed in triplicate and/or as 3 independent experiments.

Statistical Analysis

Microsoft Excel was used to calculate SDs and statistically significant differences between samples using the 2-tailed Student *t*-test. For all quantitative assays, each assay condition was performed in triplicate, and the results were repeated in at least 3 independent experiments. All data collected were subjected to statistical analysis. $P < 0.05$ was defined as statistically significant.

RESULTS

High-Frequency PEMF Stimulation Augments Early Osteogenic Marker ALP Activity

We first tested the effect of high-frequency PEMF stimulation on early osteogenic differentiation of osteoprogenitor cells. On days 3, 9, and 12 of stimulation, PEMF treatment induced a significant increase in ALP activity, most notably on day 12 (Fig. 2A), in C3H10T1/2 cells. Similarly, PEMF treatment induced a significant increase in ALP activity at days 3, 7, and 9 of stimulation in iCALs (Fig. 2B). These results indicate that high-frequency PEMF treatment enhances early osteogenic differentiation in C3H10T1/2 and iCAL osteoprogenitor cells in vitro.

High-Frequency PEMF Stimulation Induces Up-Regulation of Osteogenic Factor mRNA and Protein as Well as Increased Matrix Mineralization

We further determined the effect of high-frequency PEMF stimulation on the late stage of osteogenic differentiation. Both OCN and OPN are well-established markers of late-stage bone formation.^{20,22,25–28} Stimulated C3H10T1/2 cells were compared with

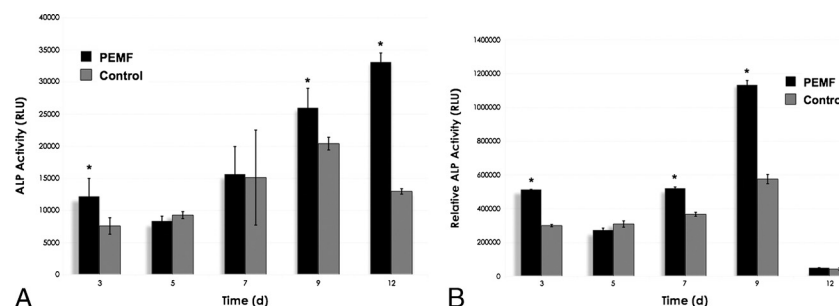


FIGURE 2. Augmentation of early osteogenic markers by PEMF stimulation. A, Alkaline phosphatase activity is a well-established marker of early osteogenic activity. Alkaline phosphatase activity was significantly elevated at days 3, 9, and 12 in PEMF-treated C3H10T1/2 cells. B, Alkaline phosphatase activity was significantly elevated at days 3, 7, and 9 in PEMF-treated iCAL cells. Data points represent the mean $\pm$ SD. Each assay was done in triplicate and/or as 3 independent experiments. * $P < 0.05$. RLU indicates relative light unit.

untreated, control cells. Semiquantitative RT-PCR of RNA extracted from treated cells demonstrated that the expression level of OCN mRNA was significantly elevated at days 7 and 10 of stimulation (Figs. 3A, B). In addition, OCN protein expression was detected in untreated cells, whereas a higher than basal level of staining was observed in PEMF-treated cells (Fig. 3C). Osteopontin expression was observed in untreated cells and to a greater extent in PEMF-treated cells (Fig. 3D). Terminal differentiation of stimulated C3H10T1/2 and iCAL cells was assessed using alizarin red S staining at day 14 of PEMF stimulation. Increased mineralization was readily detected in PEMF-treated cells (Fig. 3E). These findings suggest that high-frequency PEMF stimulation significantly promotes the late stage of osteogenic differentiation in vitro.

High-Frequency PEMF Stimulation Does Not Affect Cellular Proliferation

Previous studies investigating whether low-frequency PEMF stimulation affects cellular proliferation have reported inconsistent results.^{38,39} In the current study, neither treated nor untreated C3H10T1/2 cells reached confluency at a significantly faster rate compared with the other (Fig. 4A). Similarly, no significant difference in absorbance was observed between groups (Fig. 4A). With respect to iCALs, neither treated nor untreated cells reached confluency at a significantly faster rate compared with the other (Fig. 4B). Again, no significant difference in absorbance was observed between groups (Fig. 4B). These results indicate that high-frequency

PEMF stimulation does not significantly alter cellular proliferation or viability of C3H10T1/2 or iCAL cells.

High-Frequency PEMF-Induced Osteogenic Differentiation Is Not Solely Mediated by a Mitogen-Activated Protein Kinase-Dependent Pathway

Members of the mitogen-activated protein (MAP) kinase family of proteins have been implicated in signal transduction, stress-response pathways, and osteoblastic differentiation.^{40–44} We analyzed whether endogenous expression of 2 members of the MAP kinase pathway, p38-reactivating kinase (p38 RK or simply, p38 α) and extracellular signal-regulated kinase 1 (ERK-1), was altered in the presence of high-frequency PEMF stimulation. Using semiquantitative RT-PCR, we found that, in PEMF-treated C3H10T1/2 cells, endogenous p38 α expression was elevated compared with untreated cells at days 10 and 14 of stimulation (Fig. 5A). However, using the same RT-PCR condition, endogenous expression of ERK-1 was not altered by PEMF stimulation (Fig. 5A).

Semiquantitative analysis via densitometry was performed. The relative expression level of p38 α mRNA was modestly elevated in PEMF-treated cells at days 10 and 14 on stimulation (Fig. 5B). Compared with untreated cells, stimulated C3H10T1/2 cells expressed an increased p38 α mRNA transcript level by 50% and 30% at days 10 and 14, respectively. There was no significant difference in the relative expression level of ERK-1 mRNA in

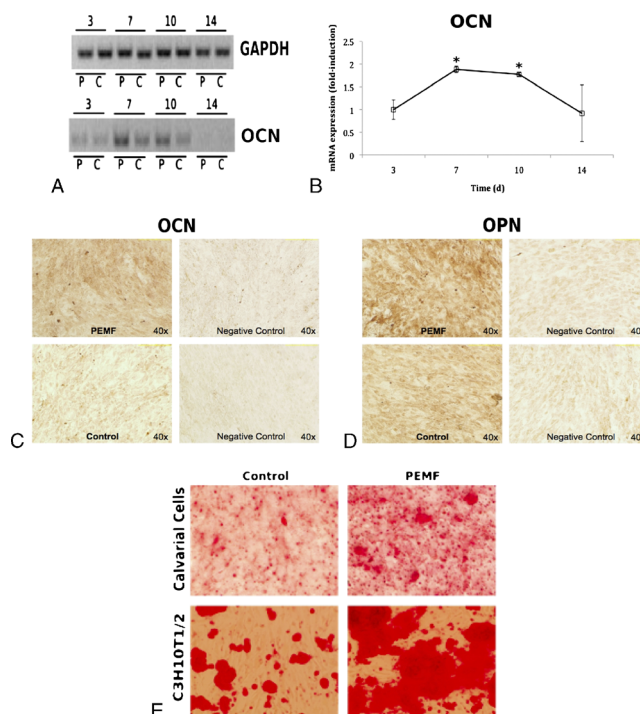


FIGURE 3. Augmentation of late osteogenic markers by PEMF stimulation. A, Endogenous expression of OCN mRNA in mesenchymal progenitor cells. Total RNA was isolated from treated and untreated C3H10T1/2 cells on days 3, 7, 10, and 14 of PEMF stimulation. Semiquantitative RT-PCR was performed using a primer pair specific for mouse OCN. The PCR products were resolved on 1% agarose gels and visualized under a UV lamp. B, Reverse transcriptase-PCR data were quantitatively analyzed by densitometry using ImageJ software and normalized to GAPDH signals obtained from the same time point. Normalized data for treated cells were then converted to fold induction by expressing the densitometric data as a ratio of treated cells to untreated cells. C, Immunohistochemical staining of OCN. C3H10T1/2 cells were stimulated by PEMFs as indicated. Expression of OCN was assessed by IHC staining analysis after 10 days of stimulation using an anti-OCN antibody (Santa Cruz Biotechnology). D, Immunohistochemical staining of OPN. C3H10T1/2 cells were stimulated by PEMFs as indicated. Expression of OPN was assessed by IHC staining analysis after 10 days of stimulation using an anti-OPN antibody (Santa Cruz Biotechnology). E, Alizarin red S staining. C3H10T1/2 cells and iCALs were stimulated using high-frequency PEMFs as indicated. Alizarin red S staining was conducted after 14 days of stimulation. Numbers in A correspond to days of stimulation. P indicates PEMF stimulated; C, control (unstimulated); Data points represent the mean $\pm$ SD. * $P < 0.05$.

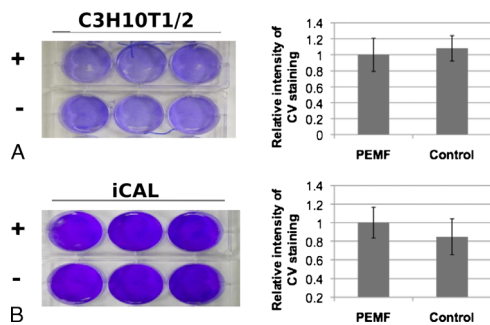


FIGURE 4. Cellular proliferation is unaffected by PEMF stimulation. A, Crystal violet viability assay. Subconfluent C3H10T1/2 cells were plated into 6-well dishes and either exposed to PEMF stimulation or not. When either PEMF-treated or untreated cells first became 100% confluent, cells from both groups were stained with crystal violet. Staining intensity was similar between both groups indicating an approximately equal number of viable cells. Crystal violet staining intensity was quantitatively assessed by dissolving the stained cells in 10% acetic acid and measuring absorbance at 570 to 590 nm. There was no significant difference in crystal violet staining intensity between the 2 groups ($P = 0.48$). B, Subconfluent iCAL cells were plated into 6-well dishes and either exposed to PEMF stimulation or not. When either PEMF-treated or untreated cells first became 100% confluent, cells from both groups were stained with crystal violet. Staining intensity was similar between both groups, indicating an approximately equal number of viable cells. Crystal violet staining intensity was quantitatively assessed by dissolving the stained cells in 10% acetic acid and measuring absorbance at 570 to 590 nm. There was no significant difference in crystal violet staining intensity between the 2 groups ($P = 0.32$). + indicates PEMF stimulated; -, unstimulated.

stimulated versus unstimulated cells (Fig. 5C). Although these results suggest that high-frequency PEMF stimulation is associated with increased p38 α mRNA expression, osteogenic differentiation began well before these changes were observed as indicated by the ALP assay and IHC staining results. It is therefore unlikely that the osteoinductive effect of high-frequency PEMF stimulation is exclusively mediated by an MAP kinase-dependent signaling cascade.

High-Frequency PEMF-Induced Osteogenic Differentiation Is Associated With BMP mRNA Up-Regulation

Members of the BMP family of proteins are known inducers of osteogenic differentiation.^{20,22,24-28,45} We analyzed whether en-

dogenous expression of osteogenic members of the BMP family⁴⁶ was altered in the presence of high-frequency PEMF stimulation. The expression of BMP-2 was slightly elevated at days 7 and 10 in PEMF-stimulated versus untreated C3H10T1/2 cells (Fig. 6A). Under the same conditions, BMP-4 expression was convincingly elevated in PEMF-treated cells at days 10 and 14 of stimulation (Fig. 6A). Bone morphogenetic protein 6 expression appeared elevated at day 3 in PEMF-treated cells and at day 14 in untreated cells (Fig. 6A). The expression level of BMP-7 was elevated at days 3 and 10 of stimulation in treated cells and appeared increased at day 7 in untreated cells (Fig. 6A). Finally, we observed that, in PEMF-treated cells, the expression of BMP-9 was increased at days 3 and 10 of stimulation (Fig. 6A).

These results are quantitatively represented via densitometric analysis of relative gene expression (Figs. 6B-F). At days 7 and 10 of stimulation, there was an increase in BMP-2 mRNA expression by 25% and 37%, respectively, in treated cells (Fig. 6B). Bone morphogenetic protein 4 mRNA expression was elevated by an average of 87% and 122% in treated cells at days 10 and 14, respectively (Fig. 6C). In treated cells, BMP-6 mRNA expression was increased by 50% and decreased by 48% compared with untreated cells at days 3 and 14, respectively (Fig. 6D). With respect to BMP-7 relative mRNA expression, treated cells expressed an average of 75% more mRNA at day 3, 20% less mRNA at day 7, and 38% more mRNA at day 10 of PEMF stimulation (Fig. 6E). Finally, there was an increase in BMP-9 mRNA expression by 78% and greater than 1000% at days 3 and 10, respectively, in PEMF-treated cells (Fig. 6F). These results indicate that high-frequency PEMF stimulation is associated with significant increases of mRNA expression of numerous BMPs.

DISCUSSION

Healing of craniofacial defects, whether due to tumor, trauma, or congenital disease, presents significant reconstructive challenges to clinicians. The criterion standard material to repair such defects is autologous nonvascularized or vascularized bone derived from the cranium, rib, iliac crest, tibia, and/or fibula.⁴⁷ However, the supply of available autologous tissue is often limited, especially in the setting of a large defect. In addition, patients may experience considerable donor site morbidity. Although various therapeutic options have attempted to solve this clinical dilemma,¹⁻⁵ they are laden with

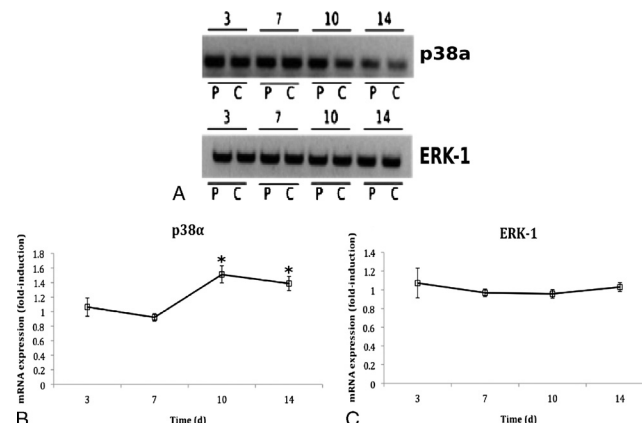


FIGURE 5. High-frequency PEMF stimulation alters MAP kinase signaling, but these changes do not appear to exclusively regulate osteogenic differentiation. A, Endogenous expression of p38 α and ERK-1 in mesenchymal progenitor cells. Total RNA was isolated from stimulated and unstimulated C3H10T1/2 cells on days 3, 7, 10, and 14 of PEMF stimulation. Semiquantitative RT-PCR was performed using primer pairs specific for mouse p38 α and mouse ERK-1. The PCR products were resolved on 1% agarose gels and visualized under a UV lamp. B and C, Reverse transcriptase-PCR data for p38 α and ERK-1 were quantitatively analyzed by densitometry using ImageJ software and normalized to GAPDH signals obtained from the same time point (Fig. 3A). Normalized data for stimulated cells were then converted to fold induction by expressing the densitometric data as a ratio of stimulated cells to unstimulated controls. Numbers in A correspond to days of stimulation. P indicates PEMF stimulated; C, control (unstimulated). Data points represent the mean $\pm$ SD. * $P < 0.05$.

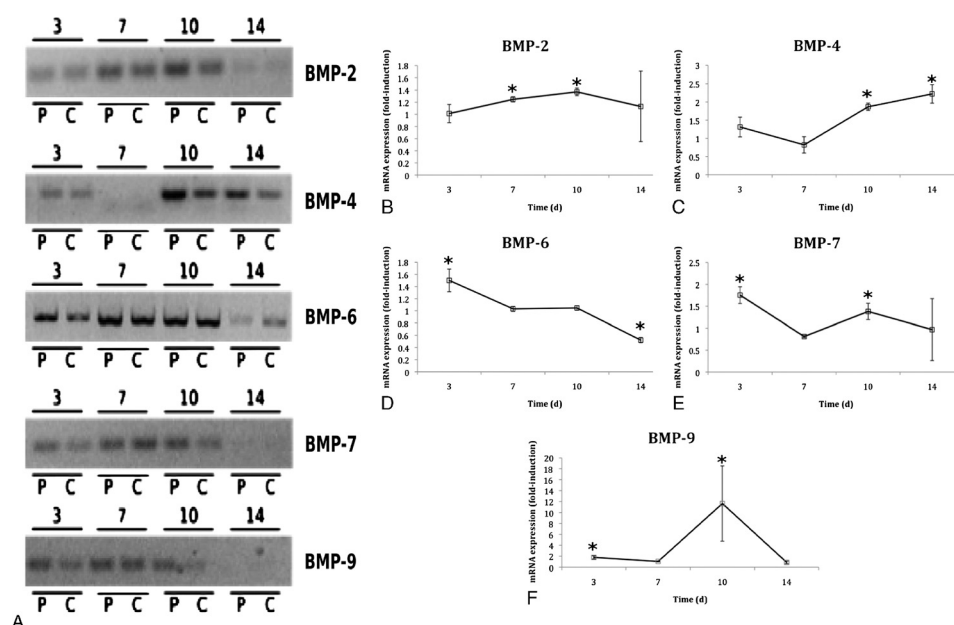


FIGURE 6. High-frequency PEMF stimulation may enhance osteogenic differentiation by inducing increased BMP expression. A, Endogenous expression of BMP-2, BMP-4, BMP-6, BMP-7, and BMP-9 in mesenchymal progenitor cells. Total RNA was isolated from stimulated and unstimulated C3H10T1/2 cells on days 3, 7, 10, and 14 of PEMF stimulation. Semiquantitative RT-PCR was performed using primer pairs specific for mouse BMP-2, mouse BMP-4, mouse BMP-6, mouse BMP-7, and mouse BMP-9. The PCR products were resolved on 1% agarose gels and visualized under a UV lamp. B–F, Reverse transcriptase–PCR data for BMP-2, BMP-4, BMP-6, BMP-7, and BMP-9 were quantitatively analyzed by densitometry using ImageJ software and normalized to GAPDH signals obtained from the same time point (Fig. 3A). Normalized data for stimulated cells were then converted to fold induction by expressing the densitometric data as a ratio of stimulated cells to unstimulated controls. Numbers in A correspond to days of stimulation. P indicates PEMF stimulated; C, control (unstimulated). Data points represent the mean $\pm$ SD. * $P < 0.05$.

disadvantages.^{48–50} Thus, continued investigation into alternative forms of bone regeneration and repair is necessary.

Tissue engineering strategies, which combine engineering technology with the principles of biology to regenerate lost or damaged tissue, have been the subject of much investigation in recent years.⁵¹ Strategies include cell- and/or growth factor–based approaches. One modality combining these 2 approaches without altering the cellular genome is biophysical stimulation. Biophysical stimulation consisting of PEMFs to stimulate bone growth, which was approved by the FDA in 1979, is still widely used for this purpose.

The effects of PEMFs on cells of the osteogenic lineage are complex and pleiotropic and have yet to be fully described. It is known that PEMF stimulation is associated with increased expression of osteogenic cytokines¹⁵ and receptors for osteogenic transcription factors,¹⁸ as well as enhanced proliferation in osteoblasts.^{17,39} However, there is great variability within the literature with respect to the effects PEMF stimulation, often due to varying methodologies used. In general, however, authors have studied only very low- or low-frequency PEMF stimulation (ie, 5–30 Hz). The current study is unique in its use of a PEMF delivery device that emits PEMFs at a frequency of 27.1 MHz.

Interestingly, previous studies have often reported that, for osteogenic differentiation to occur in the presence of low-frequency PEMFs, an additional costimulant is required. For example, Schwartz et al¹⁶ found that PEMF stimulation (15 Hz) enhances the osteogenic effects of BMP-2 on MSCs when cultured on calcium phosphate substrates. Also, culture medium is often enhanced with pro-osteogenic factors such as ascorbic acid, β -glycerophosphate, and/or dexamethasone.¹⁷ In contrast, the current study demonstrates an augmented osteogenic response to high-frequency PEMF stimulation without the aid of additional costimulants or osteogenic media. Specifically, high-frequency PEMF stimulation enhanced ALP activity as well as the expression of OCN and OPN both at the transcriptional level as well as protein level. Matrix mineralization was also

enhanced in the presence of high-frequency PEMFs. In summary, markers of early, late, and terminal osteogenic differentiation were up-regulated by high-frequency PEMF stimulation *in vitro*. Of note, cellular proliferation was not significantly altered by this form of biophysical stimulation. This is in contrast to low-frequency PEMF exposure, which has been shown to induce overexpression of proliferation markers such as c-myc and c-fos.¹⁸

This study is also unique in its use of osteoprogenitor cells rather than terminally differentiated cells of the osteogenic lineage. Whereas most authors have studied PEMF stimulation of osteoblasts, we elected to study osteoprogenitor cells as they have become important targets for bone tissue engineering because of their large quantity within humans and their ease of isolation.⁵² C3H10T1/2 cells, which are considered to retain the ability to differentiate into bone, cartilage, and fat,²⁰ displayed enhanced early, middle, and late osteogenic differentiation in the setting of high-frequency PEMF stimulation. Similarly, immortalized juvenile calvarial cells (iCALs) yielded a similar osteogenic response when stimulated. Unpublished data from our laboratory support that iCALs are in fact progenitor cells as they bear surface antigens similar to MSCs and have the ability to differentiate into multiple tissues of mesenchymal origin.

Although augmented osteogenic differentiation in the setting of high-frequency PEMF stimulation has been demonstrated in the current study, the mechanisms underlying this response remain unclear. The International Commission of Non-ionizing Radiation Protection and others have described potential mechanisms of interaction between cells and surrounding electromagnetic fields.^{53,54} These discussions, however, have been largely theoretical. Perhaps more useful from a clinical perspective is the characterization of osteogenic cytokine modulations that occur in the presence of PEMF stimulation. The MAP kinase signaling family, to which both p38 α and ERK-1 belong, has been implicated in osteoblastic differentiation and function,^{40–42,55} as well as the cellular stress-response pathway.^{43,44} We therefore evaluated whether

high-frequency PEMF stimulation alters the expression level of these proteins. We found that p38 α transcript levels were modestly elevated in stimulated cells, but that this occurred well after osteogenic differentiation had commenced. Also, we found that ERK-1 transcript levels were unchanged compared with unstimulated cells. Interestingly, the activation (phosphorylation) of p38 α has been shown to be a downstream event of BMP-mediated osteogenic induction. Noth and colleagues⁵⁶ reported that BMP-2 in particular must activate p38 α to mediate osteogenic differentiation. Data in the current study show that BMP-2 gene up-regulation is late and slightly elevated in stimulated cells, which may explain the delay and modest increase in p38 α gene up-regulation. However, it is also plausible that space limitations within the culture plates (due to morphologic changes of differentiating osteoprogenitor cells) stimulated a stress response in PEMF-treated cells, thus accounting for the rise in the level of p38 α mRNA at days 10 and 14 in these cells. Consequently, PEMF induction of osteoprogenitor cell differentiation may proceed through MAP kinase-dependent and -independent pathways. Further studies are required to more fully determine the role of MAP kinase-related factors in the cellular response to PEMF stimulation.

Bone morphogenetic proteins, which are members of the transforming growth factor β superfamily, also play an important role in osteoblast differentiation and subsequent bone formation.²⁶ Approximately 20 BMP isoforms, with varying osteoinductive potentials, have been described. Studies from our laboratory have previously demonstrated that BMP-2, BMP-6, BMP-9, and, to a lesser extent, BMP-4 and BMP-7 are the most osteogenic.^{20,25,26,46} Therefore, we evaluated whether high-frequency PEMF stimulation corresponded to modulation of these osteogenic BMPs during differentiation. We found that mRNA transcript levels of BMP-6, BMP-7, and BMP-9 were elevated in stimulated cells during the early phase of differentiation at day 3. Interestingly, mRNA transcript levels of these proteins were similar in stimulated and unstimulated cells at day 7, but again were elevated in PEMF-treated cells at day 10 (BMP-7 and BMP-9). These findings are not surprising given the role of BMPs in osteogenic differentiation. This is especially true for BMP-6, which is known to be expressed to an elevated degree early in the course of osteogenic differentiation.⁴⁶ In contrast, BMP-2 and BMP-4 mRNA expression levels were first elevated in stimulated cells later during differentiation, at days 7 and 10 (BMP-2) and days 10 and 14 (BMP-4) of stimulation. It is therefore plausible that high-frequency PEMF stimulation facilitates enhanced osteogenic differentiation of osteoprogenitor cells by inducing up-regulation of certain BMPs (eg, BMP-6, BMP-7, and BMP-9) but not others. However, further studies are necessary to evaluate if a cause-and-effect relationship between PEMF stimulation, BMP up-regulation, and enhanced osteogenesis exists.

The current study is the first, to our knowledge, to demonstrate that high-frequency PEMFs delivered by the novel device used here are capable of inducing osteogenic differentiation of murine osteoprogenitor cells. Although we found high-frequency PEMF stimulation to be associated with enhanced BMP expression, it remains unclear whether the rise in BMP mRNA levels in stimulated cells is indeed due to PEMF stimulation or due to other factors. Bone morphogenetic protein induction of cells requires phosphorylation of Smad proteins. Thus, to more definitively examine the relationship between high-frequency PEMF stimulation and BMP modulation, it would be useful to assess whether high-frequency PEMF stimulation enhances BMP receptor–Smad reporter activity and the nuclear translocation of Smad1/5/8. Similarly, whether high-frequency PEMF stimulation induces differentiation via an MAP kinase-dependent and/or -independent pathway remains in question. It is probably the case that the mechanism of PEMF induction of osteoprogenitor cell differentiation is multifactorial. Moreover, further

experiments to address the potential role of this form of biophysical stimulation in *in vivo* models of bone formation are necessary. Finally, these findings suggest that high-frequency PEMF stimulation of osteoprogenitor cells may be further investigated as an effective bone regeneration option to treat critical-size osseous defects of the craniofacial and axial skeleton.

ACKNOWLEDGMENTS

The authors thank BioElectronics for providing the high-frequency PEMF-emitting device used in the current study. The authors also thank the members of the Molecular Oncology Laboratory at the University of Chicago for their scientific and technical input during the course of the investigation.

REFERENCES

1. Acarturk TO, Hollinger JO. Commercially available demineralized bone matrix compositions to regenerate calvarial critical-sized bone defects. *Plast Reconstr Surg* 2006;118:862–873
2. Smartt JM Jr, Karmacharya J, Gannon FH, et al. Repair of the immature and mature craniofacial skeleton with a carbonated calcium phosphate cement: assessment of biocompatibility, osteoconductivity, and remodeling capacity. *Plast Reconstr Surg* 2005;115:1642–1650
3. Gosain AK, Persing JA. Biomaterials in the face: benefits and risks. *J Craniofac Surg* 1999;10:404–414
4. Sargent LA, Fulks KD. Reconstruction of internal orbital fractures with vitallium mesh. *Plast Reconstr Surg* 1991;88:31–38
5. Hurvitz KA, Kobayashi M, Evans GR. Current options in head and neck reconstruction. *Plast Reconstr Surg* 2006;118:122e–133e
6. Chen L, Jiang W, Huang J, et al. Insulin-like growth factor 2 (IGF-2) potentiates BMP-9-induced osteogenic differentiation and bone formation. *J Bone Miner Res* 2010;25:2447–2459
7. Luo J, Deng ZL, Luo X, et al. A protocol for rapid generation of recombinant adenoviruses using the adeasy system. *Nat Protoc* 2007;2:1236–1247
8. Bassett CA, Pawluk RJ, Pilla AA. Acceleration of fracture repair by electromagnetic fields. A surgically noninvasive method. *Ann N Y Acad Sci* 1974;238:242–262
9. Griffin XL, Warner F, Costa M. The role of electromagnetic stimulation in the management of established non-union of long bone fractures: what is the evidence? *Injury* 2008;39:419–429
10. Aaron RK, Ciombor DM, Simon BJ. Treatment of nonunions with electric and electromagnetic fields. *Clin Orthop Relat Res* 2004;419:21–29
11. Deibert MC, McLeod BR, Smith SD, et al. Ion resonance electromagnetic field stimulation of fracture healing in rabbits with a fibular osteotomy. *J Orthop Res* 1994;12:878–885
12. Rubin CT, Donahue HJ, Rubin JE, et al. Optimization of electric field parameters for the control of bone remodeling: exploitation of an indigenous mechanism for the prevention of osteopenia. *J Bone Miner Res* 1993;8(suppl 2):S573–S581
13. Tabrah F, Hoffmeier M, Gilbert F Jr, et al. Bone density changes in osteoporosis-prone women exposed to pulsed electromagnetic fields (PEMFs). *J Bone Miner Res* 1990;5:437–442
14. Kucharzyk DW. A controlled prospective outcome study of implantable electrical stimulation with spinal instrumentation in a high-risk spinal fusion population. *Spine (Phila, Pa 1976)* 1999;24:465–468; discussion 469
15. Bodamyali T, Bhatt B, Hughes FJ, et al. Pulsed electromagnetic fields simultaneously induce osteogenesis and upregulate transcription of bone morphogenetic proteins 2 and 4 in rat osteoblasts *in vitro*. *Biochem Biophys Res Commun* 1998;250:458–461
16. Schwartz Z, Simon BJ, Duran MA, et al. Pulsed electromagnetic fields enhance BMP-2 dependent osteoblastic differentiation of human mesenchymal stem cells. *J Orthop Res* 2008;26:1250–1255
17. Selvamurugan N, Kwok S, Vasilov A, et al. Effects of BMP-2 and pulsed electromagnetic field (PEMF) on rat primary osteoblastic cell proliferation and gene expression. *J Orthop Res* 2007;25:1213–1220

18. Lohmann CH, Schwartz Z, Liu Y, et al. Pulsed electromagnetic field stimulation of mg63 osteoblast-like cells affects differentiation and local factor production. *J Orthop Res* 2000;18:637–646
19. Kinney BM. Pulsed electromagnetic field therapy in plastic surgery. *Aesthet Surg J* 2005;25:87–91
20. Cheng H, Jiang W, Phillips FM, et al. Osteogenic activity of the fourteen types of human bone morphogenetic proteins (BMPs). *J Bone Joint Surg Am* 2003;85-A:1544–1552
21. Luo X, Sharff KA, Chen J, et al. S100a6 expression and function in human osteosarcoma. *Clin Orthop Relat Res* 2008;466:2060–2070
22. Tang N, Song WX, Luo J, et al. BMP-9-induced osteogenic differentiation of mesenchymal progenitors requires functional canonical Wnt/beta-catenin signalling. *J Cell Mol Med* 2009;13:2448–2464
23. Westerman KA, Leboulch P. Reversible immortalization of mammalian cells mediated by retroviral transfer and site-specific recombination. *Proc Natl Acad Sci U S A* 1996;93:8971–8976
24. Sharff KA, Song WX, Luo X, et al. Hey1 basic helix-loop-helix protein plays an important role in mediating BMP9-induced osteogenic differentiation of mesenchymal progenitor cells. *J Biol Chem* 2009;284:649–659
25. Kang Q, Sun MH, Cheng H, et al. Characterization of the distinct orthotopic bone-forming activity of 14 BMPs using recombinant adenovirus-mediated gene delivery. *Gene Ther* 2004;11:1312–1320
26. Peng Y, Kang Q, Cheng H, et al. Transcriptional characterization of bone morphogenetic proteins (BMPs)-mediated osteogenic signaling. *J Cell Biochem* 2003;90:1149–1165
27. Peng Y, Kang Q, Luo Q, et al. Inhibitor of DNA binding/differentiation helix-loop-helix proteins mediate bone morphogenetic protein-induced osteoblast differentiation of mesenchymal stem cells. *J Biol Chem* 2004;279:32941–32949
28. Luo Q, Kang Q, Si W, et al. Connective tissue growth factor (CTGF) is regulated by Wnt and bone morphogenetic proteins signaling in osteoblast differentiation of mesenchymal stem cells. *J Biol Chem* 2004;279:55958–55968
29. Si W, Kang Q, Luu HH, et al. CCN1/CYR61 is regulated by the canonical Wnt signal and plays an important role in Wnt3a-induced osteoblast differentiation of mesenchymal stem cells. *Mol Cell Biol* 2006;26:2955–2964
30. Kang Q, Song WX, Luo Q, et al. A comprehensive analysis of the dual roles of BMPs in regulating adipogenic and osteogenic differentiation of mesenchymal progenitor cells. *Stem Cells Dev* 2009;18:545–559
31. Bi Y, Huang J, He Y, et al. Wnt antagonist SFRP3 inhibits the differentiation of mouse hepatic progenitor cells. *J Cell Biochem* 2009;108:295–303
32. Zhu GH, Huang J, Bi Y, et al. Activation of RXR and rar signaling promotes myogenic differentiation of myoblastic C2C12 cells. *Differentiation* 2009;78:195–204
33. He BC, Gao JL, Zhang BQ, et al. Tetrandrine inhibits Wnt/beta-catenin signaling and suppresses tumor growth of human colorectal cancer. *Mol Pharmacol* 2011;79:211–219
34. Haydon RC, Zhou L, Feng T, et al. Nuclear receptor agonists as potential differentiation therapy agents for human osteosarcoma. *Clin Cancer Res* 2002;8:1288–1294
35. He BC, Chen L, Zuo GW, et al. Synergistic antitumor effect of the activated PPARGamma and retinoid receptors on human osteosarcoma. *Clin Cancer Res* 2010;16:2235–2245
36. Su Y, Luo X, He BC, et al. Establishment and characterization of a new highly metastatic human osteosarcoma cell line. *Clin Exp Metastasis* 2009;26:599–610
37. Ishiyama M, Tominaga H, Shiga M, et al. A combined assay of cell viability and in vitro cytotoxicity with a highly water-soluble tetrazolium salt, neutral red and crystal violet. *Biol Pharm Bull* 1996;19:1518–1520
38. Jansen JH, van der Jagt OP, Punt BJ, et al. Stimulation of osteogenic differentiation in human osteoprogenitor cells by pulsed electromagnetic fields: an in vitro study. *BMC Musculoskelet Disord* 2010;11:188
39. Tsai MT, Chang WH, Chang K, et al. Pulsed electromagnetic fields affect osteoblast proliferation and differentiation in bone tissue engineering. *Bioelectromagnetics* 2007;28:519–528
40. Xiao G, Gopalakrishnan R, Jiang D, et al. Bone morphogenetic proteins, extracellular matrix, and mitogen-activated protein kinase signaling pathways are required for osteoblast-specific gene expression and differentiation in MC3T3-E1 cells. *J Bone Miner Res* 2002;17:101–110
41. Lai CF, Chaudhary L, Fausto A, et al. Erk is essential for growth, differentiation, integrin expression, and cell function in human osteoblastic cells. *J Biol Chem* 2001;276:14443–14450
42. Jaiswal RK, Jaiswal N, Bruder SP, et al. Adult human mesenchymal stem cell differentiation to the osteogenic or adipogenic lineage is regulated by mitogen-activated protein kinase. *J Biol Chem* 2000;275:9645–9652
43. Zarubin T, Han J. Activation and signaling of the p38 map kinase pathway. *Cell Res* 2005;15:11–18
44. Kumar S, Boehm J, Lee JC. P38 map kinases: key signalling molecules as therapeutic targets for inflammatory diseases. *Nat Rev Drug Discov* 2003;2:717–726
45. Luu HH, Song WX, Luo X, et al. Distinct roles of bone morphogenetic proteins in osteogenic differentiation of mesenchymal stem cells. *J Orthop Res* 2007;25:665–677
46. He TC. Distinct osteogenic activity of BMPs and their orthopaedic applications. *J Musculoskelet Neuronal Interact* 2005;5:363–366
47. Tessier P, Kawamoto H, Matthews D, et al. Autogenous bone grafts and bone substitutes—tools and techniques: I. A 20,000-case experience in maxillofacial and craniofacial surgery. *Plast Reconstr Surg* 2005;116:6S–24S; discussion 92S–94S
48. Neovius E, Engstrand T. Craniofacial reconstruction with bone and biomaterials: review over the last 11 years. *J Plast Reconstr Aesthet Surg* 2010;63:1615–1623
49. Gosain AK, Chim H, Arneja JS. Application-specific selection of biomaterials for pediatric craniofacial reconstruction: developing a rational approach to guide clinical use. *Plast Reconstr Surg* 2009;123:319–330
50. Chim H, Gosain AK. Biomaterials in craniofacial surgery: experimental studies and clinical application. *J Craniofac Surg* 2009;20:29–33
51. Mistry AS, Mikos AG. Tissue engineering strategies for bone regeneration. *Adv Biochem Eng Biotechnol* 2005;94:1–22
52. Teven CM, Liu X, Hu N, et al. Epigenetic regulation of mesenchymal stem cells: a focus on osteogenic and adipogenic differentiation. *Stem Cells Int* 2011;2011:201371
53. Vecchia P, Matthes R, Ziegelberger G, et al. *Exposure to High Frequency Electromagnetic Fields, Biological Effects and Health Consequences (100 kHz–300 GHz)*. Germany Munich: International Commission on Non-ionizing Radiation Protection; 2009;16:1–392
54. Balcavage WX, Alvager T, Swez J, et al. A mechanism for action of extremely low frequency electromagnetic fields on biological systems. *Biochem Biophys Res Commun* 1996;222:374–378
55. Hu Y, Chan E, Wang SX, et al. Activation of p38 mitogen-activated protein kinase is required for osteoblast differentiation. *Endocrinology* 2003;144:2068–2074
56. Noth U, Tuli R, Seghatoleslami R, et al. Activation of p38 and smads mediates BMP-2 effects on human trabecular bone-derived osteoblasts. *Exp Cell Res* 2003;291:201–211

Use of ActiPatch Device for Treatment of Delayed Onset Muscle Soreness – Comparison to Acetaminophen and Control Group

Sheena Kong, M.D.

Introduction

Background

Delayed Onset Muscle Soreness (DOMS) is a condition associated with increased physical exertion. This condition is experienced by all individuals regardless of fitness level as it is a normal physiological response to increased exertion and the introduction of unfamiliar or strenuous physical activities. The pain caused by DOMS can impair physical training and performance, and as a result, it is of great concern to trainers, coaches, and therapists. DOMS affects many more individuals than just athletes. Many ordinary people are developing this condition as a result of excessive physical or out of the ordinary exertion. The pain and discomfort associated with this condition generally peaks at between 36 to 72 hours after an exercise routine and usually resolves within 96 hours.

For several decades DOMS had been attributed to lactic build up in the muscles after exertion. Over the past few years this assumption has been shown to be unrelated to this condition. Several research studies have indicated that lactate levels return to normal within 60 minutes post exercise. Therefore, increased lactate levels cannot cause DOMS.

DOMS is predominately caused by eccentric exercise. Connolly et al. (2003) explains that the injury that results from eccentric exercise causes damage to the muscle cell membrane, which sets off an inflammatory response. The inflammatory response leads to the formation of metabolic waste products, which act as chemical stimulus to the nerve endings that directly cause a sensation of pain and swelling.

W. Stauber et al (2000) used a high-powered microscope to analyze muscle fibers after an intense workout. Based on his research it was clear that cell membranes were ruptured and other structural components were disrupted; however, damage to the muscle fibers is relatively small. This damage is not limited to one area but occurs throughout the muscle fiber. This microscopic muscle damage causes an inflammatory response. It is this inflammatory response that causes muscle soreness due to: 1) the accumulation of fluid (swelling) and 2) chemicals secreted by white blood cells that activate pain receptors (Smith, 1991).

While there has been some research conducted on the treatment of DOMS, no particular treatment option has been proven to be dominant in treating or preventing the condition. The most popular intervention is pharmacological options using non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. Stretching and warm-up exercises as well as nutritional augmentation via supplements have also been explored with varying degrees of success.

NSAIDs, such as aspirin and ibuprofen, and acetaminophen are popular treatments for DOMS, but some of the research conducted in this area is inconclusive. Additionally, there are significant concerns associated with negative potential side effects such as gastrointestinal distress, liver toxicity and related coronary issues.

There has been considerable research relative to using nutritional supplementation as a potential treatment for DOMS with particular emphasis on vitamins E and C and other antioxidants, which are thought to reduce the proliferation of free radicals generated during an inflammatory response. These effects are inconclusive as are other investigations into use of L-carnitine.

While neither NSAIDs nor nutritional supplements have been proven to reduce the onset of DOMS, there has been some research suggesting that simple warm-up exercises can meaningfully reduce the onset of the condition. Szymanski (2003) introduced the “repeated-bout effect” as a way to reduce DOMS. The repeated-bout is a progressive adaptation to exercise that has been shown to consistently reduce DOMS and exercise induced damage to muscles.

ActiPatch is a miniaturized medical device that delivers continuous electromagnetic therapy to restore damaged cells. The device is a Class III medical device that is available only through a licensed health care practitioner in the United States. The device, however, is widely available on an over-the-counter basis outside of the United States. Significant clinical data shows that ActiPatch reduces edema, inflammation and pain. ActiPatch uses a mild electrical current and radiofrequency waves at a frequency that stops the release of pain and inflammatory mediators, increasing blood flow, and reestablishing normal cell interaction.

Pulsed electromagnetic stimulation (PEMF) in some form has been used or investigated since the early 1930s. There is a large body of clinical experience that has realized its value as an effective treatment for tissue trauma, particularly in the early stages of inflammation. Numerous studies are available that document its effectiveness in orthopedic surgery, arthritis, and even plastic surgery (breast augmentation). While no study has demonstrated the complete elimination of pain, PEMF has shown less dependence on medications and some enhancement of the recovery period. Also, there has not been a single study showing any harmful effects so it is safe to conclude that PEMF is safe for human use.

The precise mechanism by which PEMF works on controlling pain after injury is not known. It is theorized that it may affect pain levels by its effect of nitric oxide (NO) release, a short-lived signaling molecule in the anti-inflammatory cascade. It is also suggested that it has an effect on stabilizing cell membranes such that the edema phase of an injury is more rapidly resolved.

ActiPatch devices function at a frequency in the 27.1 MHz ISM band and are confined within the field of the patch’s loop antenna. The patch induces electric current in human tissue, but it is oscillating at such a high frequency that it cannot be detected by the patient. The high frequency results in a depth of penetration into the tissues of approximately 10 cm. When the patch is used over a 24 hour period, it produces an absorbed energy of 630 mJ/cc which is well within the range of effectiveness for soft tissue injuries. The patch produces a power density at the

skin surface between 14 and 73 $\mu\text{W}/\text{cm}^2$ and induces an electrical field of about 10 milliVolt/cm, resulting in adsorbed power levels in the range of 7.3 $\mu\text{W}/\text{cm}^3$. This provides field exposure levels at the target tissue that are five to nine orders of magnitude above the thresholds which have been established for non-thermal electromagnetically induced biological effects at the cell and tissue level.

The ActiPatch uses proven medical technology to truncate the human body's natural inflammatory response breaking the cycle of chronic inflammation. ActiPatch does this by delivering pulsed electromagnetic energy directly to the affected area and driving out the edematous fluid along with byproducts of the damaged tissue. The affect is a well-documented and a significant overall improvement in the restorative and recovery process following injury resulting in a substantial reduction in the pain associated with soft tissue injury. These statements are supported by multiple studies, but no specific research has been done relative to its effects on DOMS.

ActiPatch was cleared by FDA in 2002 for the treatment of edema following blepharoplasty. Clinical data presented by BioElectronics to Health Canada resulted in its approval for relief of pain in musculoskeletal complaints, and the product is now available over-the-counter throughout Canada. The product is also cleared for over-the-counter sales in European Union countries and other countries throughout the world.

Study Execution

Study Design

- This was an observational study to evaluate the treatment of delayed onset muscle soreness.
- Study participants were placed randomly into one of three groups 1) a control group, 2) a group that utilized ActiPatch, and 3) a group that received over-the-counter strength acetaminophen
- 102 participants in total - 38 used the ActiPatch, 38 acting as control, and 26 used acetaminophen
- Sample size for acetaminophen group was smaller due to resistance from participants to consume acetaminophen
- Age range from 18 to 35, subjects were healthy collegiate athletes and trainers who exercise regularly and participate in team sports
- Interventions were approximately 20 sets of 10 repetitions of bicep resistance exercises using free weights to induce DOMS in the bicep muscles of both arms
- Approximately 48 hours post exercise, participants returned to study site and were given a PainRecording Scale (Visual Analogue Scale) sheet to record their perceived level of DOMS pain in their bicep muscles.

Exclusion Criteria

- Anyone who is unable to give consent or document written consent in English
- Anyone who is confirmed or who could possibly be pregnant

- Anyone with allergy or intolerance to acetaminophen
- Anyone with known active liver disease

Recruitment of Participants

Participants were recruited from collegiate athletic teams and athletic training personnel.

Randomization

After the DOMS inducing resistance exercise regiment was completed, each study participant was randomly assigned to one of the three participating groups. Study participants assembled randomly in a straight line. The number of participants in the line was divided by three. Starting left to right of the line the three groups were selected with the first third becoming the ActiPatch group, second third becoming the control group and the final third becoming the acetaminophen group.

Adverse Events Reporting

As described in the informed consent forms, all adverse events were to be reported to the investigating physician or the collegiate athletic training personnel. Participants were given the direct phone number to the principal investigator. No adverse events were reported to either the principal investigator or the collegiate athletic training personnel.

Data Collection

Measurements of DOMS-related muscle pain assessments were done by the participants who completed a simple form that recorded pain and muscle soreness levels on the VAS line. The data was collected by the athletic training personnel under the supervision of the principal investigator. The principal investigator transferred the data to a spreadsheet from which statistical analysis was performed.

Statistical Analysis

Data was collected from the participants approximately 48 hours after the administration

of the DOMS inducing resistance exercise regiment using a VAS (Visual Analogue Score) pain assessment.

Statistical Analysis

Data were collected at the end of the study. The monitor copied the data from the individual sheets and placed in a spreadsheet with one entry per participant depending on the participant's particular group, i.e., Tylenol, Control or ActiPatch. Thus there were three columns, one for each group. At the end of the study, the data were provided for analysis.

The data were analyzed using Excel macro's. Means, variances and standard deviations for the VAS scores were calculated for each subsample. The difference between cell means was tested using t-tests with the following formula:

$$t = \frac{\bar{X}_T - \bar{X}_C}{\sqrt{\frac{\text{var}_T}{n_T} + \frac{\text{var}_C}{n_C}}}$$

where $\bar{X}$ is the mean for the group, VAR is the variance of the observations, n is the sample size and the subscripts T and C represent the two different groups being compared, e.g. "treatment" and "control" group.

Acceptance Criteria

This study used two tailed tests and significance levels of .05, .025 and .001 to determine the significant differences in sample means.

Results

102 patients were enrolled in this study, 38 using the ActiPatch, 38 acting as control, and 26 using Tylenol. Table 1 shows the mean VAS scores for each subsample along with the variances for these means, i.e., var/n .

Table 1: Group Means and Variances

	Tylenol	Control	ActiPatch
Means	2.507	3.179	1.500
Means Variance	.1315	.1678	.0620

Table 2 presents the results of the individual t-tests. Comparisons were made between ActiPatch and the control group and ActiPatch and the Tylenol group. The former comparison was significant at the .001 level; the latter was significant at the .05 level.

Table 2: t-test statistics

	t-statistic	degrees of freedom	significance level
ActiPatch vs. Control	3.504	78	.001
ActiPatch vs. Tylenol	2.290	64	.05

Discussion

The data from this study demonstrates the ActiPatch device manufactured by BioElectronics Corporation had a significant effect on reducing DOMS-related symptoms of muscle pain and soreness when compared to both a control group that received no treatment and a group that was treated with 1 gram of acetaminophen in the form of Extra Strength Tylenol. Based on this data, the principal investigator concludes that ActiPatch is safe and effective treatment for DOMS.

The use of ActiPatch seems to be a convenient, safe and effective new treatment for muscle pain and soreness, especially when compared to currently FDA approved over the counter treatments, such as acetaminophen, NSAIDs and other pain medications that may have questionable safety profiles.

A Randomized, Double-Blind Study Evaluating the Safety and Efficacy of Allay Menstrual Pain Therapy in the Treatment of Primary Dysmenorrhea

Investigators: Barry L. Eppley, M.D., D.M.D. & Sheena Kong, M.D. (June 2009)

Prepared: June 2009

Revision History: September 2010

Indication: Pain and Edema Resulting from Menstruation

Sponsor: BioElectronics Corporation
4539 Metropolitan Court
Frederick, MD 21704

Study Number: BIEL-002

Phase of Development: N/A

Study Start Date: 15 January 2009 (First Subject Enrolled)

Study End Date: 15 May 2009 (Last Subject Results Recorded)

Primary Investigators: Sheena Kong, M.D. & Barry Eppley, M.D., D.M.D.

Responsible Medical

Monitor: Barry Eppley, M.D., D.M.D.

Report Date: June 2009

This study was conducted in accordance with the guidance of Good Clinical Practice (GCP), including archiving of essential documents.

Title
A Randomized, Clinical Study Evaluating the Safety and Efficacy of Allay Menstrual Pain Therapy in the Treatment of Primary Dysmenorrhea
Investigators
Multicenter; refer to Appendix A for a complete listing of investigators and locations.
Study Centers
Two centers in the United States enrolled subjects in this clinical study. One center was located in San Francisco, CA, (SF) and the other in Indianapolis, IN (IN)
Publications
None
Study Period
15-Jan-09 15-May-09
Objective
The objective of this study was to characterize the risks, effectiveness, and benefits of using Allay Menstrual Pain Therapy for the treatment of primary dysmenorrhea.
Methodology
A prospective randomized double-blind, placebo- and positive-controlled study of Allay Menstrual Pain Therapy versus placebo in adult women for primary dysmenorrhea. The study was randomized in a 1:1 ratio at the time of enrollment to receive either an active Allay device or a placebo device.
Number of Subjects (Planned and Analyzed)
Planned: 70 Total Subjects, at least 30 Placebo, 30 Active Analyzed: 91 Indianapolis: 47 San Francisco: 44
Diagnosis and Main Criteria for Inclusion
Women ages 18-35 suffering from (self-diagnosed) moderate to severe pain and discomfort resulting from menstruation. Persons who do not have implanted medical devices (ie. cardiac pacemakers, implantable cardioverter defibrillators (ICD), neurostimulators, etc.). Persons who have not undergone abdominal surgery.
Duration of Treatment
One menstrual cycle (5-7 days), one month. Subjects were instructed to wear the device continuously for at five to seven consecutive days from the onset of their menstrual cycles. Subjects were also instructed to remove the device before coming into con

Investigational Product, Dose and Mode of Administration
ActiBand, Pulsed Electromagnetic Field Therapy (PEMF). Power Source: 3.5 V Battery; Carrier Frequency: 27.1 MHz; Pulse Width: 100 microseconds; Pulse Repetition Frequency: 1KHz
Reference Therapy
None
Criteria for Evaluation:
Efficacy: Self-reported levels of pain Safety: Safety and Tolerability Outcome Measures: Quality of life; Subjective (perceived) pain relief, Symptoms Questionnaire Data, Comment Card
Statistical Methods:
Control: Patients self-reported perceived levels of pain for each day of their menstrual cycle prior to participation in the clinical trial. Efficacy: Self-reported levels of pain during the trial were compared to the control, and statistics were collected on the percentages of pain reduction on a per-patient basis to normalize the data. Safety: Adverse events were assessed. The safety data summary includes all participants who wore the device at least one day. Outcome Measures: Quality of life, Adherence Questionnaire Data, Treatment Satisfaction

SUMMARY OF RESULTS

Introduction

Primary Dysmenorrhea, commonly referred to as menstrual cramping, is a medical condition characterized by pain from contractions in the lower abdomen occurring at the onset of menstruation in the absence of an identifiable pelvic disease. Sharp pains in the lower abdomen begin at the start of menstruation and may continue for up to 3 or 4 days. The pain can range from mild to severe and can often interfere with many normal activities. While the majority of women who have menstrual periods experience some discomfort, an estimated 10% or more are temporarily disabled by the high level of pain that they experience. It is distinguished from secondary dysmenorrhea, which refers to painful menses resulting from pelvic pathology such as endometriosis.

Many different treatment strategies have been tried for menstrual pain but the most commonly used are non-steroidal anti-inflammatory drugs. (NSAIDS) Despite drug therapy, universal relief is not obtained and some patients experience gastric upset and other minor problems with NSAID use.

Pulsed electromagnetic field (PEMF) therapy in some form has been used or investigated since the early 1930s. There is a large body of clinical experience that has realized its value as an effective treatment for tissue trauma, particularly in the early stages of inflammation. Numerous

studies are available that document its effectiveness in orthopedic surgery, arthritis, and even plastic surgery (breast augmentation, rhinoplasty, etc.). While no study has demonstrated the complete elimination of pain or need for some medication relief, PEMF has shown less dependence on medications and some enhancement of the recovery period. Also, no known studies have reported adverse or harmful effects so it is fair to conclude that PEMF is safe for human use.

The precise mechanism by which PEMF works on controlling pain after injury is not known. It is theorized that it may affect pain levels by its enhancement of nitric oxide (NO) release, a short-lived signaling molecule in the anti-inflammatory cascade. It is also suggested that it has an effect on stabilizing cell membranes such that the edema phase of an injury is less or more rapidly resolved.

Allay menstrual patches have been specifically developed for application over the uterine area. The looped design functions at a frequency in the 27.1 MHz ISM band and is confined within the field of the patch's loop antenna. The patch induces electric current in human tissue but is oscillating at such a high frequency that it cannot be detected by the patient. The high frequency results in a depth of penetration into the tissues of approximately 10 cm. When the patch is used over a 24 hour period, it produces an absorbed energy of 630mJ/cc, which is well within the range of effectiveness for soft tissue injuries. The patch produces a power density at the skin surface between 14 and 73 μ W/cm² and induces an electrical field of about 10 mV/cm, resulting in adsorbed power levels in the range of 7.3 μ W/cm³. This provides field exposure levels at the target tissue that are five to nine orders of magnitude above the thresholds which have been established for non-thermal electromagnetically induced biological effects at the cell and tissue level.

Results

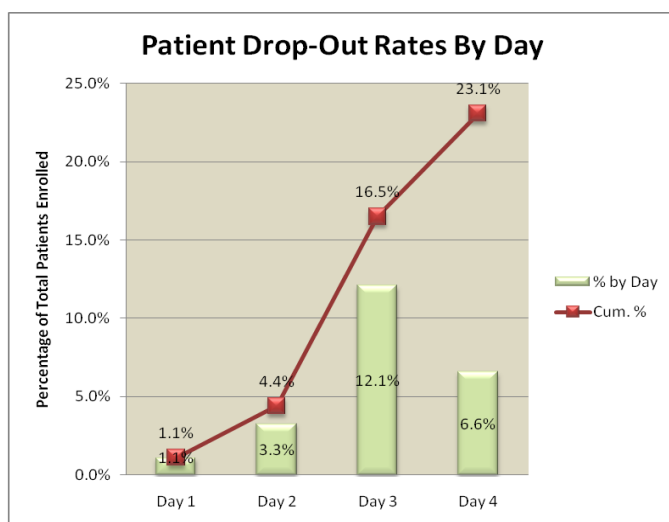
A total of ninety-one (91) women were enrolled with moderately severe dysmenorrhea and were randomly assigned an active or control Allay Menstrual Pain Therapy device. Forty-eight (48) patients received active devices while the remaining forty-three (43) received placebo devices. The patients ranged in age from 18-34 years, with an average age of 26.2. Seventy-five percent (75%) of the subjects were White and fifteen percent (15%) of the subjects were Asian. A further breakdown is included below:

<i>Patient Age Range:</i> 18-34	Average Age
Indianapolis	28.6
San Francisco	24.9
Active Group	27.3
Placebo Group	27.8
	26.2

	IN	SF	Total
Active	23	25	48
Placebo	24	19	43
Total	47	44	91

Race	Qty	%
White	68	74.73%
Black	7	7.69%
Hispanic	2	2.20%
Asian	14	15.38%
	91	

Twenty-one (23.1%) subjects discontinued prematurely. However, 95% of subjects remained in the study for Days 1 and 2 (most severe days) of their menstrual cycles. Seven percent discontinued use due to wear issues (indicated below), and five percent discontinued use because their pain was eliminated. Although the data shows that ten percent of participants indicated that they discontinued use because the device didn't help their menstrual pain, this statistic includes the individuals given the placebo patch.



Drop-out Rates						
	IN	SF	Total	% by Day	Cum. Drop-Outs	Cum. %
Day 1	1	0	1	1.1%	1	1.1%
Day 2	1	2	3	3.3%	4	4.4%
Day 3	5	6	11	12.1%	15	16.5%
Day 4	3	3	6	6.6%	21	23.1%

Reasons Indicated for Drop-Out		
Pain Was Eliminated	4	4.4%
Adverse Events	0	0.0%
Wear Issues	7	7.7%
Device Didn't Help	9	9.9%
Lost Device	1	1.1%
Other	-	-

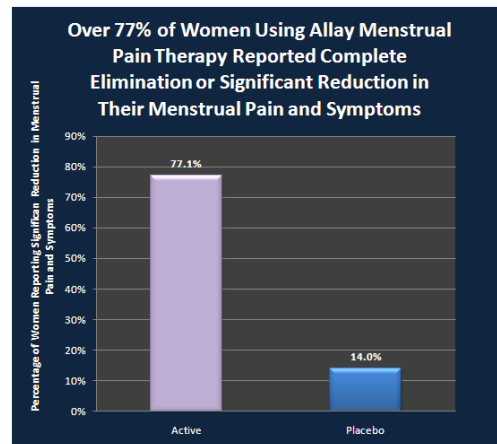
Device Wear Issues	Qty	% of Study Participants
Moistness	2	2.20%
Irritation	1	1.10%
Placement Stability	7	7.69%
Total	10	10.99%

Efficacy Results

This clinical study evaluating Allay Menstrual Pain Therapy showed that 77.1% of women using the active Allay patch reported either complete elimination or reduction in their typical menstrual pain and discomfort. Within this group, 17 (35.4%) reported least a 50% reduction in pain.

	Composite Pain Score				
	Estimated Percentage Pain Relief (Average)				
		# Patients			
	%	Active	Placebo	Active	Placebo
Positive Responders	0-10% (no change)	11	37	22.92%	86.05%
	10-25%	9	6	18.75%	13.95%
	25-50%	11		22.92%	
	50-75%	14		29.17%	
	75-100%	3		6.25%	
	Totals	48	43	100.00%	1

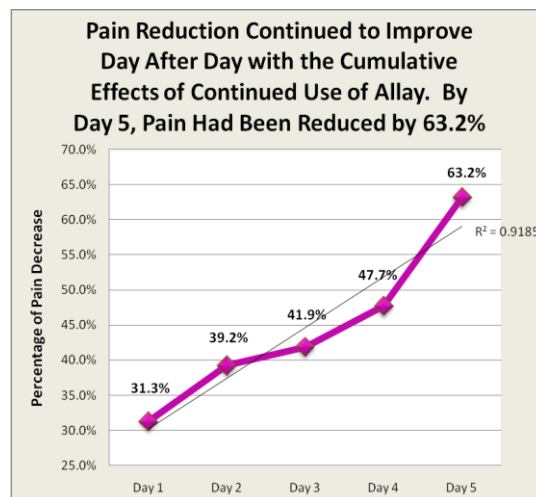
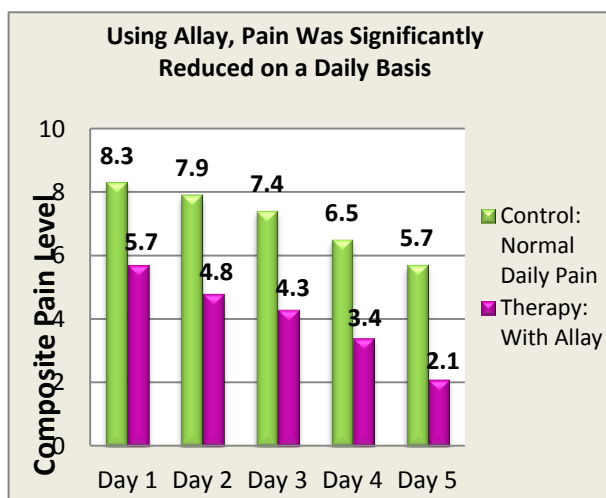
	Active	% of Active	Placebo	% of Placebo
Negative Responders	11	22.9%	37	86.0%
Positive Responders	37	77.1%	6	14.0%
Totals	48		43	



Relative to the active group, in the placebo (control) group, six studies (13.95%) reported a reduction in their menstrual pain symptoms. The differences in positive response to either the active or control device was of statistical significance ($p < 0.05$).

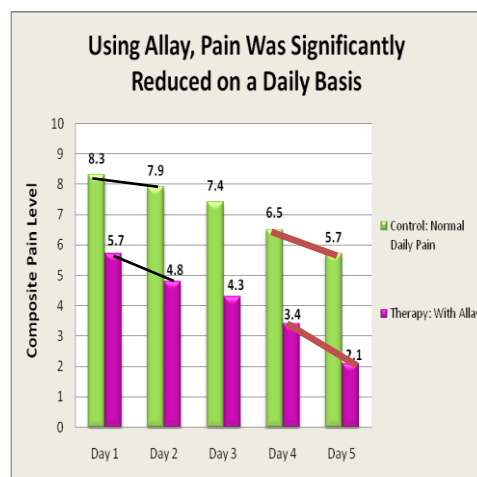
Although the actual levels of pain indicated are subjective and vary by patient, the change in pain levels is the leading factor in determining efficacy. On average, pain was decreased significantly on a daily basis, as indicated in the table and charts below. The clinical results also indicate that over time the percentage of decrease in pain increases, suggesting that there is a strong correlation between duration of use of Allay and pain reduction. By Day 5, pain had been reduced by 63.2%, compared to a reduction of 31.3% on Day 1.

	Control: Normal Daily Pain	Therapy: With Allay	% Decrease in Pain
Day 1	8.3	5.7	31.3%
Day 2	7.9	4.8	39.2%
Day 3	7.4	4.3	41.9%
Day 4	6.5	3.4	47.7%
Day 5	5.7	2.1	63.2%



Although this correlation is also affected by the body's natural tendency to reduce pain over time, the pain levels were significantly lower with use of Allay, and the rate at which pain decreased was significantly higher at the onset and end of patients' menstrual cycles. For instance, from Day 1 to Day 2, pain decreased at a rate of 1.25x the body's perceived normal rate of pain reduction.

	Control: Normal Daily Pain	Diff	Therapy: With Allay	Diff	% Decrease in Pain	Rate Increase of Pain Reduction
Day 1	8.3		5.7		31.3%	
Day 2	7.9	0.4	4.8	0.9	39.2%	125.0%
Day 3	7.4	0.5	4.3	0.5	41.9%	0.0%
Day 4	6.5	0.9	3.4	0.9	47.7%	0.0%
Day 5	5.7	0.8	2.1	1.3	63.2%	62.5%



The overall slopes of -0.66 and -0.86 for normal and Allay pain decrease, respectively, also suggest that pain may be reduced at a slightly faster rate overall with use of Allay, although not statistically significant.

Safety Results

One subject discontinued early from slight irritation, but there was no evidence of a clinically significant effect. No (zero) subjects experienced adverse events.

Adverse Events	0
----------------	---

Outcome Measure Results

Satisfaction with treatment was qualitatively assessed by subject-reported patience adherence, treatment satisfaction, and symptoms questionnaire. Comments are included in Appendix A.

Conclusion

The clinical study demonstrates that the Allay Menstrual Pain Therapy is an effective and safe non-drug method for use in the treatment of primary dysmenorrhea. Allay can be offered as a primary, drug-free treatment method for women suffering from moderate dysmenorrhea. In more severe cases of dysmenorrhea, it can be an adjuvant treatment to reduce the duration of use or the amount of other oral medications.

Discussion

Menstrual cramps and pain are the result of contractions of the uterus. Prostaglandins stimulate the uterine muscles to contract and shed its lining. Women who have high levels of prostaglandins will experience more intense contractions of their uterus and subsequently more pain. The benefit of anti-inflammatory medications is directed towards modulating one's responsiveness to prostaglandin levels. Unfortunately, anti-inflammatory medications are not always completely effective at relieving menstrual pain and they have well-known side effects as well. A non-drug alternative would be a novel approach to the treatment of menstrual pain and would address a significant unmet need.

This clinical study has demonstrated that the Allay menstrual patch is effective at reducing and/or ameliorating the pain from dysmenorrhea. It is statistically significant that the active patch group exhibited a 77% positive response compared to just a 9% positive response in the placebo. It does so with no reported side effects other than some wear issues undoubtedly related to the design or material issues of the patch.

The exact mechanism by which the PEMF of the Allay patch works for menstrual pain is currently speculative. Certainly, the placebo enhancement effect plays a role but that alone cannot exclusively account for the study results, particularly in the face of such a discrepant and very low positive response to the control group patches. Modulation of pain pathways is one potential explanation Pain signals are transmitted along nerve cells to pre-synaptic terminals.

PEMF has been shown to result in pre-synaptic terminals that have slowed release of neurotransmitters by altering membrane potentials thus blocking or reducing pain signals. Another potential mechanism is the well-known anti-inflammatory PEMF by affecting T-cell activity and inflammatory mediator releases. It is likely that the cumulative effect of all of these three different mechanisms accounts for the positive responses seen.

PEMF therapy appears to have a role in the management of pain from dysmenorrhea which is currently dominated by pharmaceutical and some surgical treatments. PEMF offers a noninvasive approach with no side effects and no potential for drug interactions.

Physician Conducted Pilots and Testimonials.

ActiPatch and Rapid Recovery Breast Augmentation Study (Dr. Barry Eppley, M.D.)

Contemporary recovery after breast augmentation is designed to be short with minimal disruption of one's lifestyle. Anti-inflammatory medications and early physical therapy of the arms (the attachments of the pectorals muscle) are the mainstays of an aggressive recovery program after the placement of breast implants. Gone are the need for bulky dressings and restrictions on physical activity after surgery which had been the hallmarks of breast implant surgery in the past. The less pain a patient has, the more physical therapy they can do to further expedite their return to normal activities of daily living. In an effort to control pain after breast augmentation, I often employ pulsed electromagnetic therapy using ActiPatch topical patches devices. To determine whether this was actually beneficial or just a psychotherapeutic concept, a prospective clinical study of breast augmentation patients was done.

A prospective clinical study of forty-eight (48) women undergoing breast augmentation was conducted from November 2007 to November 2008. Women underwent breast augmentation with either saline or silicone breast implants through a transaxillary (saline) or inframammary (silicone) incision. Patients were aware that they would receive ActiPatch therapy as part of their postoperative protocol. At the completion of surgery, ActiPatch devices (crescent-shaped) were placed over the medial and superior aspect of the breasts (over the pectorals muscle) and taped into position inside their surgical bra. For the first twenty patients, the device was activated (activating tab pulled) on the left breast and on the opposite right breast the device was not activated. (activating tab was trimmed but not pulled) The patients were not informed which devices were which. In the next twenty-eight patients, the device locations were reversed. Patients were instructed to wear the devices for the first seventy-two hours after surgery after which they were to be discarded. Patients were given a sheet to complete at the time of discontinuing their ActiPatch therapy so that they could rate their postoperative pain on a simple scale (1 - 10) and, most importantly, compare and rate the pain between the two breasts at that time period.

In the first twenty patients, fourteen rated the active device breast as less uncomfortable than the control patch side. In the next twenty-eight patients, twenty-one rated the active side less painful. In total, thirty-five patients (73%) reported less pain and more comfort ability on the breast that received pulsed electromagnetic therapy than on the control side.

Pulsed electromagnetic therapy has been around for a long time and its potential benefits are based on creating an anti-inflammatory effect. ActiPatch provides a simple, low-cost method of delivery of this potential healing technology. In this breast augmentation study, ActiPatch demonstrated less pain within the first few days after surgery. Given its ease of use and lack of any potential for creating any adverse problems, its use as part of a breast augmentation recovery protocol appears to have offer patients some real benefits.

While all pain studies are flawed, and this one is no exception, it certainly suggests that pulsed electromagnetic therapy (PEMT) should be further explored. A change in the design of the device so that it 'fits' the breast better may be even more useful. A large round loop that would fit around the circumference of the breast is more likely to deliver the effects of PEMT to the breast in a more even distribution although I could argue that the pain after breast augmentation is muscular rather than 'breast' in origin.

ACTIPATCH - A New way of treatment, Pilot investigation of 52 patients in general praxis.

Evaluated September – October 2008

Jørn Bennedbæk, MD

Hypothesis of treatment

In living healthy cells the potential of the membrane potential is stable equals rest potential. The inside of the membrane is negative in relation to the outside. Most of our cells have a rest potential in the membrane in the range about 70 millivolt. When it increases it is hyperpolarized, if it decreases the membrane will depolarise. If the 70 millivolt is valued as a field over the 7 nanometer thick membrane, the strength of the field equals 10.000 volt pr.mm. Changes in the environment/field has direct effect on conformation of proteins in the plasma membrane and due to this abilities of the composition of multi formations of amino acid (ref. 1) The synthesis of proteins in fibroblasts in electromagnetic fields has been investigated earlier (ref.2)

ActiPatch uses the modulated radio frequencies generated electromagnetic field to induce the low-frequent membrane stabilizing pulse, with amplitude in the field of 1 kHz / 100 uV/cm the membrane will due to this, be forced to re-establish the rest potential.

The effect can be at more points. Stabilizing the cell. Improvement of Cell-to-cell communication. Improvement of the neuron-transmission. The direct and indirect effect in inhibition of the inflammation process at all levels.

Duration of treatment

The patients received instructions in use with application from bedtime until morning every day for one week. The effect had to be noted on a visual scale from 0-5, where (vs5) is maximal (start) pain and (vs0) no-pain. Duration of the test was 7 days.

Diagnosis and results

3 patients with fascitis pedis. 1 pain free after 5 days, 1 after 6 days No..3 was on stage (vs1) after 7 days.

7 patients with epicondylitis lateralis. 1 was free of pain day 4, 4 on day 6, and 1 had only slight pain (vs2) on day 7. 1 * had no effect.

2 patients with epicondylitis medialis had no pain, whatsoever on day 6.

4 patients with tibialis anterior syndrome. 2 were free of pain after 3 days and 2 on day 5 .

2 patients with Mb.Osgood-Schlatter had no effect after 7 days.

2 patients with pes anserinus tendinitis had only slight problems on day 7 dage (vs1)

3 patients with polyartrosis manuum verified also as arthritis rheumatoides . 2 had no pain after 6 days, 1 had only slight problems on day 7 (vs2)

2 patients with arthritis urica. On day 7 one had only slight pain (vs1) and the other had moderate pain (vs3)

8 patients with myosis lumbale et paravertebrale without referred pain or neurological deficits. 3 had no pain on day 4 ,2 on day 5 . 1 on day 6. and 2 had only slight problems on day 7 (vs2)

2 patients with pain one year after surgery for cervical prolaps of discus. No effect.

2 patients with pain one year after surgery for lumbal prolaps of discus .1 had moderate pain day 7 (vs2) 1 had no effect.

3 with distorsio pedis/laesio lig. talofibulare anterior. 2 had no pain day 6. 1 had day 7 only slight problems (vs1)

8 patients with various tendinites of wrest /forehand and antebrachium (flexors and brachioradialis). 4 had no pain day 3. 1 on day 4 1 on day 5 and 1 on day 6.dag. 1 had no effect .

4 patients with tendinitis of Achilles. 3 had no pain day 5 .1 on day 6.

* Had earlier operation on pronator teres syndrome bilateralis.

Discussion

AP has proved convincing effect at many conditions. There were neither side-effects reported nor complaints of any kind. The device is simple and easy to handle.

Spontaneous remission would appear at more of the patients in this investigation, but how fast in relation to these results?

2 patients with rheumatoid arthritis concluded the relief of pain just as effective as the treatment of steroids in high-dose for short periods, but faster effect.

In this pilot project, application was only 8 hours per day. The device may and can be used 24 hours per day. Could more of the patients have effect faster or some at least have had an effect if the device were used permanently. AP has power for 720 hours. The primary impression in effect of the treatment of patients with the diagnosis, where positive response has been notified is effect at least as effective as usually treatment, but with far faster onset of relief. AP has cell restitution effect and more test has been started in examination of wound healing and effect on post-operations conditions (healing process, haematoma etc.) and latest in treatment of psoriasis.

ActiPatch has been in use on more patients with ulcers of the lower limbs treated by nurses in the county.

Furthermore the joint pains of one psoriasis patient disappeared after 1 week of treatment. When stopped the joint pain came back after few days. Disappeared again with re-use of the AP for few days

More injuries from sport has been treated with AP and has proved excellent results. Many questions now and in the future will be asked in order to examine further possibilities and effects of the AP. Further investigation on a scientific basis has to be done to find right indications of treatment and duration of the many diseases potentially involved.

References

1. Suhr-Jessen, Peter (2004) Basis bog i Cellebiologi
2. McLeod, K.J., Lee, R.C., and Ehrlich, H.P. (1987) Frequency dependence of electric field modulation of protein synthesis in fibroblasts. Science 236: 1465-1469

ActiPatch Therapy Following Cosmetic Surgery of the Face and Neck: A Valuable Adjunct to the Postoperative Management

Casas, Laurie A., MD FACS

ActiPatch Therapy has become an integral part of the postoperative treatment plan/regime in my patients following Blepharoplasty, Rhinoplasty, Facelift, Neck lift and Liposuction of the Neck. After completing a Prospective Observational Study which evaluated the effects of using ActiPatch on 32 patients (52 procedures) as compared to a control group of 30 patients (45 procedures) who underwent the same cosmetic procedures without the use of ActiPatch, we found that ActiPatch Therapy decreased postoperative swelling, bruising, localized fibrosis and localized discomfort by 30-50%. Because of this Observational Study I have added ActiPatch

Therapy to my postoperative protocol for patients undergoing cosmetic surgical procedures of the face and neck and who desire a decrease in their postoperative recovery time.

I performed a prospective observational study on 32 patients (52 procedures) using ActiPatch Therapy and compared them to 30 patients (45 procedures) control group to evaluate the effect of ActiPatch on postoperative 1) swelling and bruising, 2) localized subcutaneous fibrosis and 3) localized discomfort. Both groups of patients were on the same preoperative protocol of vitamin supplements and postoperative protocol which continued the use of supplements and added the use of Cox 2 inhibitors for localized pain. In addition, all patients had Manual Lymphatic Drainage with a specific protocol of 2 visits per week for 6 weeks. Both groups of patients were evaluated by a Nurse Practitioner, the treating physical therapist and the senior author at 3 days, 5-6 days, 7-10 days, 13-14 days, 21 days, 28 days and 42 days postoperatively. An observational data sheet was completed at each visit which documented 1) localized pain, 2) swelling and bruising, 3) the soft tissue fibrosis which is characterized by subcutaneous lumps and tightness and discomfort when moving the operated part. The ActiPatch was either placed under the gauze head wrap dressing in the facelift, neck lift and neck liposuction patients, and at the glabella or corner of the brow in the Rhinoplasty and Blepharoplasty patients. All patients used the ActiPatch for the first three days and some continued to use it for a total of ten days. The endpoint was when all visible bruising had resolved.

We found that ActiPatch therapy was very effective in decreasing postoperative swelling and bruising. Specifically, our observers noted a 30-50% reduction in the number of days the patients had visible swelling and ecchymosis compared to the control group. Both groups had Manual Lymphatic drainage and Deep Tissue Release Therapy scheduled for 2 times per week for six weeks.(ref: "Manual Lymphatic Drainage: An Integral Component of Postoperative Care in the Plastic Surgery Patient" Presented at the Annual Conference of the American Society of Lymphology, Chicago, IL August 1999 and "The role of Manual Lymphatic Drainage in the Postoperative Care of Cosmetic Plastic Surgery Patients", Presented at the Annual Conference of the American Society of Lymphology, Las Vegas, Nevada October,2004.) The ActiPatch group required 30-50% fewer sessions to decrease swelling, bruising and localized discomfort from soft tissue fibrosis. The endpoint of Lymphatic Drainage Therapy is decided by both the patient and the therapist who together decide that the operated tissues feel and look normal.

ActiPatch Therapy is very useful to decrease the swelling, bruising and localized discomfort in patients undergoing cosmetic of the face and neck. The following protocol is now used in my practice for all patients who desire a decrease in their postoperative recovery time following Cosmetic Surgery of the face and neck.

Blepharoplasty: ActiPatch 500 either over each eyebrow, or at the corner of each brow or under each lower eyelid. 24 hours per day for 3-7 days. It is removed for showering and replaced by moistening the hydrogel. Some patients used paper tape to help hold the ActiPatch in position.

Rhinoplasty: ActiPatch 500 at the Glabella 24 hours per day for 3-7 days.

Facelift: ActiPatch 500 is placed on each preauricular area under the gauze head wrap dressing. When the dressing is removed the ActiPatch is placed either in the pre or post

auricular area as the swelling drops down the face to the neck lymph nodes over the first 3-10 days after surgery.

Neck Lift: ActiPatch 500 is placed on both sides of the neck under the ear and under the gauze head wrap dressing. When the dressing is removed the ActiPatch is worn on the neck are where the most swelling and bruising is visible for the first 3-10 days.

Neck Liposuction: same protocol as Neck Lift.

ActiPatch is removed for showering and replaced by moistening the hyrogel. Some patients use paper tape to help hold the ActiPatch in position.

Abdominoplasty Post-Operative Pain Control with ActiPatch

Kimberley B.C. Goh, M.D.

An abdominoplasty is one of the most painful cosmetic body contouring procedures we perform. Fear of post-operative pain has always been an obstacle for patients when considering an abdominoplasty. There is now a new, portable, lightweight and low cost way to decrease postoperative pain. The ActiPatch is a device which produces pulsed electromagnetic therapy that helps reduce swelling relieve pain and enhance healing.*

I have been using the ActiPatch 500 for postoperative abdominoplasties for about six months and have been very impressed at its pain control. Prior to ActiPatch I had been using oxycodone and diazepam for postoperative pain control with intra-operative marcaine placed under the flap prior to emergence from anesthesia. The patients complained of significant pain and usually needed additional prescriptions for both pain and muscle relaxers within four days of surgery and often again at one week. Since using ActiPatch postoperatively I have not written a supplemental prescription for pain control and they have some left over. Their narcotic and medication needs have now decreased approximately seventy five percent.

Initially four patients were placed on ActiPatch for pain control after abdominoplasties. All patients had standard abdominoplasties with muscle and skin tightening; one had an augment performed as well. The charts were reviewed and interviews performed retrospectively to the physician to evaluate postoperative pain and narcotic use.

The first patient, A., was a 44 year old woman who had three full term pregnancies and several months of nursing. She complained of loss of breast fullness and a saggy abdomen. Physical exam revealed ptosis and pseudoptosis of her breasts and a lax abdominal wall, especially the upper abdomen, and loose skin on the upper and lower abdomen. She underwent a standard abdominoplasty and a bilateral subglandular breast augment. The breast augment was performed using a smooth round saline Mentor implant 350cc filled to 400cc in subglandular position through an inframammary incision. The abdominoplasty resected about 40 X 13 centimeters of skin, and the diastasis recti was corrected (about an eight centimeter plication). Fourteen cc of 1/4% marcaine was placed under the flap at closure. As the patient was emerging from anesthesia the ActiPatch 500 was placed on the epigastrium and attached using its adhesive pad directly on the skin.

In recovery she needed one oxycodone for immediate postoperative pain. The evening of surgery she rested comfortably, and on her first visit on postoperative day one she came for her appointment wearing makeup with her hair styled and had minimal complaints of pain. She had been taking only one oxycodone every six hours because she was afraid that it would hurt, but had no complaints of abdominal pain. She had her oxycodone changed to mepergan because of nausea, but used very little her first week. She said she felt "she could have run a marathon" and could not believe how little pain she had.

Patient B was a 30 year old woman with two full term pregnancies who complained of a lax abdomen after multiple pregnancies and a previous cesarean section five years prior. She

underwent a standard abdominoplasty. Of note is that she had undergone a scheduled knee surgery two days prior to her abdominoplasty in order to make her recovery simultaneous. At surgery she had a 14 X 46 centimeter skin resection and an eight centimeter tightening of her diastasis recti. Fifteen cc of 1/4% marcaine was placed under the flap at closure. The ActiPatch 500 was activated and placed directly on the epigastrium after the wound was closed. In recovery she had one oxycodone given orally. The first evening postop she used less than one oxycodone and one diazepam every six hours. The first day postop she complained only of knee pain, and felt that the abdominoplasty was less painful than her previous cesarean section. She also came in wearing facial cosmetics and had her hair styled on her first day after surgery. Her first week post op she also used less than 20 each of diazepam and oxycodone.

Patient C was a 33 year old nulliparous woman with a previous submuscular augment mastopexy who complained of inability to tighten her lower abdomen with diet and exercise. She underwent a standard abdominoplasty with resection of approximately 13 centimeter by 43 centimeter skin ellipse, and an eight centimeter diastasis recti plication. Postoperatively she had an ActiPatch 500 activated and applied to her epigastrium. In the recovery room she had one oxycodone orally for pain. The evening of surgery she took one and one 5 mg diazepam. By the evening of surgery her only pain was on moving to stand or recline. At rest she was pain free and reported less pain than her previous augment mastopexy. The following week she took one or two oxycodone a day.

Patient D was a 56 year old with one full term pregnancy who was interested in improving her saggy lower abdomen. She had a previous lower midline incision for a cesarean section and a right lower quadrant incision for a bone graft donor site. She had significant diastasis recti and a small abdominal pannus. She underwent a standard abdominoplasty with repair of diastasis and right lower quadrant plication for asymmetrical laxity. She had a 15 X 42.5 skin resection and a six centimeter plication. She had 12 cc of 1/4% marcaine placed prior to emergence under the flap. Postoperatively she had one ActiPatch 500 device placed on the epigastrium. In the recovery room she had one oxycodone, and the first evening of surgery, one diazepam and one oxycodone. The next few days she was taking one to two diazepam once a day and one oxycodone four times a day. By the end of her first week she had taken about twenty of the oxycodone and even less of the diazepam.

The amount of pain relief with the ActiPatch after a major surgery is impressive. This retrospective review of patients' charts and interviews demonstrates a marked decrease in postoperative pain and use of narcotics in abdominoplasty. While the ActiPatch can assist with healing and reduce swelling, those benefits are difficult to appreciate in actual clinical practice. The amount of pain relief however is easier to evaluate. There is a marked decrease in the use of pain medications and as well as a significant increase in comfort level. It is currently a low cost, small, portable, narcotic free pain control device, and should be considered in all major abdominal surgeries.

Appendix

A table of publications which have used PRFE therapy at 27.12MHz to treat medical conditions:

Date	Injury - pain	Publication
1971	Oral surgery	Aronofsky, D. H. (1971). Reduction of dental postsurgical symptoms using nonthermal pulsed high-peakpower electromagnetic energy. <i>Oral Surg. Oral Med. Oral Pathol.</i> 32:688–696.
1978	Oral surgery	Hutchinson, D., Witt, S., Fairpo, C. G. (1978). Pulsed electromagnetic energy therapy in third molar surgery. <i>Oral Surg. Oral Med. Oral Pathol.</i> 46:748–754.
1981	Oral surgery	Rhodes, L. C. (1981). The adjective utilization of Diapulse therapy (pulse high peak power electromagnetic energy) in accelerating tissue healing in oral surgery. <i>Quart. NDA</i> 39:166–175.
1968	Foot surgery	Kaplan, E. G., Weinstock, R. E. (1968). Clinical evaluation of diapulse as adjunctive therapy following foot surgery. <i>J. Amer. Podiat. Assoc.</i> 58:218–221.
1985	Foot surgery	Santiesteban, A. J., Grant, C. (1985). Post-surgical effect of pulsed shortwave therapy. <i>J. Amer. Podiatr. Med. Assoc.</i> 75:306–309.
1982	Breast augmentation surgery	Silver, H. (1982). Reduction of capsular contracture with two-stage augmentation mammoplasty and pulsed electromagnetic energy (Diapulse therapy). <i>Plast. Reconstr. Surg.</i> 69(5):802–808.
2008	Breast augmentation surgery	Heden, P., Pilla, A. A. (2008). Effects of pulsed electromagnetic fields on postoperative pain: a double-blindrandomized pilot study in breast augmentation patients. <i>Aesthetic Plast. Surg.</i> 32:660–666.
2010	Breast reduction surgery	Rohde, C., Chiang, A., Adipoju, O., et al. (2010). Effects of pulsed electromagnetic fields on interleukin-1beta and postoperative pain: a double-blind, placebo-controlled, pilot study in breast reduction patients. <i>PRS</i> 125:1620–1627.
2002	Mastectomy surgery	Mayrovitz, H. N., Sims, N., Macdonaki, J. (2002). Effects of pulsed radio frequency diathermy on postmastectomy arm lymphedema and skin blood flow: a pilot investigation. <i>Lymphology</i> 35:353–356.
1982	Blepharoplasty surgery	Nicolle, F. V., Bentall, R. M. (1982). Use of radio-frequency pulsed energy in the control of postoperative reaction in blepharoplasty. <i>Aesthetic Plast. Surg.</i> 6:169–171.
1975	Orchidopexy	Bentall, R. H. C., Eckstein, H. B. (1975). A trial involving the use of pulsed electro-magnetic therapy on children undergoing orchidopexy. <i>Zeitschrift fu'r Kinderchirurgie</i> 17(4):380–389.
1983	Hand injury	Barclay, V., Collier, R. J., Jones, A. (1983). Treatment of various hand injuries by pulsed electromagnetic energy (Diapulse). <i>Physiotherapy</i> 69:186–188.
1974	Acute ankle inversion	Wilson, D. H. (1974). Comparison of short wave diathermy and pulsed electromagnetic energy in treatment of soft tissue injuries. <i>Physiotherapy</i> 60:309–310.
1993	Grade I-II ankle sprains	Pennington, G. M., Danley, D. L., Sumko, M. H., et al. (1993). Pulsed, non-thermal, high-frequency electromagnetic energy (DIAPULSE) in the treatment of grade I and grade II ankle sprains. <i>Mil. Med.</i> 158:101–104.
1978	Ankle and foot injury	Pasila, M., Visuri, T., Sundholm, A. (1978). Pulsating shortwave diathermy: value in treatment of recent ankle and foot sprains. <i>Arch. Phys. Med. Rehab.</i> 59:383–386.
2002	Heel pain	Shandles, I. D. P., J., Reynolds, K. L. (2002). Heel Neurooma: the egigma of recalcitrant heel pain and an innovative approach highlighting sixty surgical cases and areview of two hundred and fifty seven symptomatic but non-surgical cases. <i>Foot</i> 12:10–20.
1985	Lateral ankle sprain	Barker, A. T., et al. (1985). A double-blind clinical trial of low power shortwave therapy in the treatment of soft tissue injury. <i>Physiotherapy</i> 71:500–504.
2003	Acute calcaneal fracture	Buzzard, B. M., Pratt, R. K., Briggs, P. J., et al. (2003). Is pulsed shortwave diathermy better than ice therapy for the reduction of oedema following calcaneal fractures?: Preliminary trial. <i>Physiotherapy</i> 89: 734–742.
1990	Long-term neck pain	Foley-Nolan, D., Barry, C., Coughlan, R. J., et al. (1990). Pulsed high frequency (27 MHz) electromagnetic therapy for persistent neck pain. A double blind, placebo-controlled study of 20 patients. <i>Orthopedics</i> 13:445–451.

1992	Acute whiplash injury	Foley-Nolan, D., Moore, K., Codd, M., et al. (1992). Low energy high frequency pulsed electromagnetic therapy for acute whiplash injuries. A double blind randomized controlled study. <i>Scand J Rehabil Med</i> 24:51–59.
2006	Osteoarthritis (knee)	Jan, M. H., Chai, H. M., Wang, C. L., et al. (2006). Effects of repetitive shortwave diathermy for reducing synovitis in patients with knee osteoarthritis: an ultrasonographic study. <i>Phys. Ther.</i> 86: 236–244.
2005	Osteoarthritis (knee)	Laufer, Y., Zilberman, R., Porat, R., et al. (2005). Effect of pulsed short-wave diathermy on pain and function of subjects with osteoarthritis of the knee: a placebo-controlled double-blind clinical trial. <i>Clin. Rehab.</i> 19:255–263.
2005	Osteoarthritis (knee)	Callaghan, M. J., Whittaker, P. E., Grimes, S., et al. (2005). An evaluation of pulsed shortwave on knee osteoarthritis using radiolucosintigraphy: a randomized, double blind, controlled trial. <i>Joint Bone Spine</i> 72:150–155.
1988	Osteoarthritis (weight bearing joint)	Svarcova, J., Trnavsky, K., Zvarova, J. (1988). The influence of ultrasound, galvanic currents and shortwave diathermy on pain intensity in patients with osteoarthritis. <i>Scand. J. Rheumatol.</i> 67:83–85.
1964	orthopedic	Cameron, B. M. (1964). A three phase evaluation of pulsed, high frequency, radio short waves (Diapulse): 646 patients. <i>Amer. J. Orthop.</i> 6:72–78.
1991	posttraumatic algoneurodystrophies	Comorosan, S., Pana, I., Pop, L., et al. (1991). The influence of pulsed high peak power electromagnetic energy (Diapulse) treatment on posttraumatic algoneurodystrophies. <i>Rev. Roum. Physiol.</i> 28:77–81.
1989	Perineal trauma post child birth	Grant, A., Sleep, J., McIntosh, J., et al. (1989). Ultrasound and pulsed electromagnetic energy treatment for perineal trauma. A randomized placebo-controlled trial. <i>Br. J. Obstet. Gynaecol.</i> 96:434–439.
1964	Surgical wound healing	Cameron, B. M. (1964). A three phase evaluation of pulsed, high frequency, radio short waves (Diapulse): 646 patients. <i>Amer. J. Orthop.</i> 6:72–78.
1981	Skin grafts	Goldin, J. H., Broadbent, N. R., Nancarrow, J. D., et al. (1981). The effects of Diapulse on the healing of wounds: a double-blind randomized controlled trial in man. <i>Br. J. Plast. Surg.</i> 34:267–270.
1995	Pressure ulcers	Salzberg, C. A., Cooper-Vastola, S. A., Perez, F. J., et al. (1995). The effects of non-thermal pulsed electromagnetic energy (Diapulse) on wound healing of pressure ulcers in spinal cord-injured patients: a randomized double-blind study. <i>Wounds</i> 7(1):11–16.
1999	Pressure ulcers	Kloth, L. C., Berman, J. E., Sutton, C. H., et al. (1999). Effect of pulsed radio frequency stimulation on wound healing: a double-blind pilot study. In: Bersani, F. <i>Electricity and Magnetism in Biology and Medicine</i> (pp. 875–878). New York: Academic/Plenum.
1996	Pressure ulcers	Seaborne, D., Quirion-DeGirardi, C., Rousseau, M., et al. (1996). The treatment of pressure sores using pulsed electromagnetic energy (PEME). <i>Physiother. Cancer</i> 48:131–137.
1991	Stage II-III pressure ulcers	Itoh, M., Montemayor, Jr, J. S., Matsumoto, E., et al. (1991). Accelerated wound healing of pressure ulcers by pulsed high peak power electromagnetic energy (Diapulse). <i>Decubitus</i> 4:24–25, 29–34.
1995	Stage II,III and IV decubitus ulcers	Tung, S., Khaski, A., Milano, E., et al. (1995). The application of diapulse in the treatment of decubitus ulcers: case reports. <i>Contemp. Surg.</i> 47:27–33.
2008	Complex diabetic foot wounds	Larsen, J. A., Overstreet, J. (2008). Pulsed radio frequency energy in the treatment of complex diabetic foot wounds. <i>J. WOCN</i> 35(5): 523–527.
2008	Stage III and IV pressure ulcers	Porreca, E. G., Giordano-Jablon, G. M. (2008). Treatment of severe (stage III and IV) chronic pressure ulcers using pulsed radio frequency energy in a quadriplegic patient. <i>Eplasty</i> 8:e49.
2009	Chronic wounds	Frykberg, R., Tierney, E., Tallis, A., et al. (2009). Cell proliferation induction: healing chronic wounds through low-energy pulsed radiofrequency. <i>Int. J. Low Extrem. Wounds</i> 8:45–51.
2011	Venous stasis ulcers	Fletcher, S. (2011). Successful treatment of venous stasis ulcers with combination compression therapy and pulsed radio frequency energy in a patient scheduled for amputation. <i>J Wound Ostomy Continence Nurs</i> 38, 91-94.
2011	Chronic wounds	Rawe, I.M., and Vlahovic, T.C. (2011). The use of a portable, wearable form of pulsed radio frequency electromagnetic energy device for the healing of recalcitrant ulcers: A case report. <i>Int Wound J.</i>
2010	Chronic wound registry	Frykberg, R.G., Driver, V.R., Lavery, L.A., Armstrong, D.G., and Isenberg, R.A. (2011). The Use of Pulsed Radio Frequency Energy Therapy in Treating Lower Extremity Wounds: Results of a Retrospective Study of a Wound Registry. <i>Ostomy Wound Manage</i> 57, 22-29.
2011	Chronic cutaneous wounds	Maier M. Pulsed radio frequency energy in the treatment of painful chronic cutaneous wounds: a report of two cases. <i>PainMed.</i> 2011 May;12(5):829-32

Market Clearances of BioElectronics Product Range

Country	Allay™	ActiPatch®	RecoveryRx™
All European Union Countries	✓	✓	✓
Korea		✓	
Italy	✓	✓	✓
Canada	✓	✓	✓
Nigeria	✓	✓	✓
Iran	✓	✓	✓
Jordan	✓	✓	✓
Kuwait	✓	✓	✓
Columbia	✓	✓	✓
Peru	✓	✓	✓
New Zealand	✓	✓	✓
Australia	✓	✓	✓
United States			✓

Testimonials

Actual reviews from Amazon.co.uk

4 of 4 people found the following review helpful

★★★★★ 5.0 out of 5 stars **Works better than medication, no side effects.** 1 Jun 2012
By **Jonathan punski**

This review is from: Neck, Shoulder & Hip Pain Relief Therapy with Multi-use Adhesives - Provides long lasting pain relief (Misc.)

I used this product on my back and upper shoulder, and it provides a soothing comfort when applied, which continues to last even once it is removed. Well worth the money.

2 of 2 people found the following review helpful

★★★★★ 5.0 out of 5 stars **Great pain reliever,** 23 Aug 2012
By **Chloe**

This review is from: Neck, Shoulder & Hip Pain Relief Therapy with Multi-use Adhesives - Provides long lasting pain relief (Misc.)

This is great for those who have back/shoulder pain from sitting for too long. I highly recommend it for its effectiveness especially the price is reasonable.

1 of 1 people found the following review helpful

★★★★★ 5.0 out of 5 stars **It really works** 24 May 2012
By **Bowler**

This review is from: Wrist & Elbow Pain Relief Therapy - Provides long lasting pain relief

I have to say I was a little skeptical but I said what the heck it's only a few bucks and now Im totally hooked. Say bye to pain meds

★★★★★ 5.0 out of 5 stars **heel pain** 1 Aug 2012
By **Phil**

This review is from: ActiPatch Smart Insole Heel Pain Relief Therapy Women's - Provides long lasting heel pain relief

Heel pain relief smart insole is great the best i have tried, tried lots but this one works , it costs a lot but worth it .

Date	Rating	Comments
------	--------	----------

10/09/2012	5	Excellent customer service! Superb communication! Will buy again.
30/08/2012	5	Bought this product and was doubtful at first.....but the

Testimonials

		doubts went away when I started to use and I never felt this good before when it's that time of the month so many thanks.....will be buying again thanks
25/08/2012	5	Does the job. Actually worked for me after wearing it overnight. And again when the pain got back - a night is all it takes (so far)
23/08/2012	5	GREAT
21/08/2012	5	These were as described and arrived on time. Not sure whether they have made much difference to my plantar fasciitis but they are comfortable to wear.
20/08/2012	5	Finally something that works....pain free for the Mrs. which means no more headaches for me lol
14/08/2012	5	Excellent service and product
24/06/2012	5	Item is excellent and highly recommended. Seller was prompt in delivery.
24/06/2012	5	Great service, great product

Actual reviews from Amazon.com

5.0 out of 5 stars **can't live without it**, March 12, 2012

By **andajaja**

Amazon Verified Purchase

This review is from: BioElectronics Acti-Patch ActiPatch Back Square Healing Recovery Patch (Health and Beauty)

This is the only thing out of many that has helped my "pain" I've been to doctors and pain clinics; tried shots and pills and nothing has helped me like this acti-patch, i wear it every hour I'm home and sleep with it I'm on my second one and getting better all the time, i think it will finally heal me one day, I've been having this pain now for over 25 years so i don't expect a cure in a few months. This is a great product and i thank dr. Oz for putting me on to it.

0 of 1 people found the following review helpful

4.0 out of 5 stars **Great Product!** February 25, 2012

By **Wendi**

This review is from: BioElectronics Acti-Patch ActiPatch Back Square Healing Recovery Patch (Health and Beauty)

I think this product works great!!! I have had lower back pain and to relieve it, I first put on Sombra and then I use the Acti-Patch... I can definitely tell a difference than just using the Sombra alone. I like that you can use it again and again. (vs. those heat packs you can only use for 8 hours-- which actually burned my skin).

★★★★★**Works better than medication, no side effects.**, 1 Jun 2012

By **Jonathan Punski**

Testimonials

This review is from: ActiPatch Pain Relief Therapy - Multi-use Adhesives - Drug-Free & Clinically Proven (Misc.)

I used this product on my back and upper shoulder, and it provides a soothing comfort when applied, which continues to last even once it is removed. Well worth the money.

★★★★★Works great...great service !, March 17, 2011

By Christopher B. Barry (Marin County, CA USA)

Amazon Verified Purchase(What's this?)

This review is from: BioElectronics Acti-Patch Actipatch Knee Healing Recovery Patch (Health and Beauty)

Product arrived as state brand new and great price. Great customer service. Thought I ordered two pieces and wrote email, got a phone call in literally 2 minutes clearing it up.

★★★★★Great product, October 15, 2010

By Djones

Amazon Verified Purchase

This review is from: Actipatch Wrist / Ankle or Foot Pain Therapy Bioelectronics acti-patch pain patch recovery (Health and Beauty)

This is a great product that really works. Would be nice if it was available in the US over the counter. Much better than popping pills for pain relief. Really speeds up the healing process. I would highly recommend this product.

★★★★★It Work for me., September 22, 2010

By Edgar

Amazon Verified Purchase

This review is from: Actipatch Pain Therapy -Bioelectronics acti-patch Heel pain patch (Health and Beauty)

For over 2 months,I had pain in my ankle and I was not relieved until I bought the patch. And with only 4 days 24hrs of use, I can walk better and I have no pain. I recomend it.

★★★★★jewelers delight, August 7, 2010

By mister123 "curious cat" (watertown n.y.)

This review is from: Actipatch Wrist / Ankle or Foot Pain Therapy Bioelectronics acti-patch pain patch recovery (Health and Beauty)

i am an optician by trade and jeweler by hobby!! alot of fine detaled work that wears greatly on my thumbs and wrist! great relief from this patch!! i would ache after a long session of fabricating glasses or fine soldering jewelery !! now after a long period of work

Testimonials

i put on the patch and over night i wake up with no stiffness or aching.would recommend to anyone.

★★★★★Actipatch works!!!!, April 28, 2010

By Tom Cat (Seven Hills, OH)

Amazon Verified Purchase

This review is from: Actipatch Pain Therapy -Bioelectronics acti-patch Heel pain patch (Health and Beauty)

I am writing this under my wife's account since she is the one that bought it for me. After years of athletics/activities (Baseball/basketball/volleyball/racketball and skiing among other things) had finally taken their toll on my joints, my left ankle especially was starting to throb continually. I had always been extremely active but had to finally stop all of these activities due to the discomfort I was experiencing. Even normal daily walking was beginning to be uncomfortable. After seeing these products noted in the Wall Street Journal Innovation Awards my curiosity was aroused but I will admit to being skeptical at the time. She surprised me by buying me the heel pain patch last week for a try. The box sat on the table for several days before I finally decided to try it. Within a day my ankle was almost pain free, and as noted by others, I was walking around with the patch on, not even aware that it was there. Plus, I was no longer popping Ibuprofen several time a day.

The down side is that the wrap cloth used to hold the unit needs to be more robust and secure, plus the on/off mechanism needs to be improved. Hopefully Bioelectronics will address these issues, however, I would still recommend trying this product to anyone.

★★★★★IT WORKS, February 3, 2010

By Phil Serraino "Man in blue" (Westchester NY)

Amazon Verified Purchase

This review is from: Actipatch Pain Therapy -Bioelectronics acti-patch Heel pain patch (Health and Beauty)

I had some plantar facitis pain for several months, used the acti patch and after the second day, I noticed less pain. Going on a week now and the tightness in the plantar is almost dissipated. Can't wait until I get up in the morning with no pain. Non invasive and reasonably priced and serves its purpose well.

★★★★★Skeptic, now totally convinced!, January 24, 2010

By Mel (Seattle, WA United States)

This review is from: BioElectronics Acti-Patch Actipatch Knee Healing Recovery Patch (Health and Beauty)

Testimonials

I'm an off-again on-again jogger. I haven't been able to run much in recent years, because when I do, I get severe knee pain, and nothing has helped with it. It is a chronic problem. Well, at the start of the new year, I was going to start running again, and had heard about the Actipatch product so I decided to order one to have it ready for when the knee pain returned. I was a skeptic for 2 reasons: 1) nothing has ever helped my knee pain, and 2) when the product arrived, it was "cheap" looking (the on/off "switch" is not optimal, and the straps to hold the product in place are worthless. So, I ran 8 miles yesterday, and last night, I could barely walk, the knee pain was so bad. I put the Actipatch in place when I went to bed. This morning, I was TOTALLY amazed, but I have absolutely ZERO knee pain. None. I am stunned.

The product design could use some improvement (particularly the on/off mechanism). It does come with an ace bandage that works fine to hold the patch in place, so it's really OK that the "straps" are useless.

But really, I don't care what this thing looks like. It works. It works better than I would have ever dreamed. Maybe I'll be able to run more after all. I couldn't be more pleased!

I know this company makes patches for pain relief of other body parts as well. If I had other aches and pains, I wouldn't hesitate to order those patches as well. This thing is awesome.

★★★★★**In a place far far away....., January 8, 2010**

By C. Curtis

This review is from: Actipatch Wrist / Ankle or Foot Pain Therapy Bioelectronics actipatch pain patch recovery (Health and Beauty)

I am a contractor in Iraq and I hurt my hand doing my work. I did wear one of those wrist braces for a little bit but that was annoying so I ordered the wrist patch to see if it could help. Well a long story short it worked great and I stopped wear anything. One issue I have is the construction of the patch is a tad cheap but not anything too bad but this is a review and thats the only thing I noticed

★★★★★**Great Product with some flaws, January 2, 2010**

By C. Curtis

Amazon Verified Purchase

This review is from: BioElectronics Acti-Patch Actipatch Knee Healing Recovery Patch (Health and Beauty)

I love this product I bought the wrist one before and it worked great so when my knee started hurting from running alot I thought why not try the knee one. It did exactly what it said it would do and my knee pains are gone. So now I will talk about the flaws I wish the patch was just a tad higher quality it is a great product but the construction seems cheap. I have never had one fall apart but it is just something I noticed about it and sense this is a review I want to be honest about it good or bad.

Testimonials

★★★★★IT WORKS!, December 13, 2009

By demon "demon" (Brooklyn, New York)

This review is from: Actipatch Wrist / Ankle or Foot Pain Therapy Bioelectronics acti-patch pain patch recovery (Health and Beauty)

My friend has repetitive strain injury in the ball of the thumb right where this wrist patch is designed for, so I'm going to get one for her. I have been surfing for over 25 years, and lower back pain is very common with experienced surfers. I don't like using tylenol or advil - I just don't like the cumulative effect these drugs probably has on my body.

Acupuncture or chiropractic manipulation can help, but both are really expensive. I tried the larger actipatch for lower back with an open mind, and I am soooo glad I did - this thing is AWESOME! I put it on after a hot shower before I hit the sack, and when I woke 8 hours later there was already big improvement. I was just hanging out for the day so I kept it on, and by the end of the day I could do backflips - the pain was completely gone. This thing works AND it's non-invasive. Couldn't ask for better - we only get one body, and we need to take care of it. A+ for this product.

★★★★★FINALLY relief that works!, November 30, 2009

By demon "demon" (Brooklyn, New York)

This review is from: Actipatch Pain Therapy -Bioelectronics acti-patch Heel pain patch (Health and Beauty)

I do some jogging and have some kind of stone bruise under my heel - or I've pulled something. I have used the larger actipatch for lower back pain and I am soooo glad I did - it is AWESOME! That is why I don't hesitate in recommending this foot and ankle patch. I don't like using tylenol or advil - I just don't like what the cumulative effect these drugs probably have on my body. Acupuncture or chiropractic manipulation can help, but both are expensive, so this is a great alternative - more importantly it works AND it's non-invasive! Couldn't ask for better - we only get one body, and we need to take care of it. A+ for this product.

★★★★★Great product. worked well., October 20, 2009

By Justin M Call "josey" (NC)

This review is from: Actipatch Pain Therapy -Bioelectronics acti-patch Heel pain patch (Health and Beauty)

I'm a medical provider, so I don't give my recommendation lightly.

I used this for an entirely different purpose than indicated, but the ankle patch was on sale!

I used this for elbow joint pain from my olecranon bursitis.

In fact, I have the patch on now. It has worked surprisingly well, which is... well... a surprise. I only ordered this on a whim after doing a little research into PEMF technology.

Just something extra, given that my Ibuprofen wasn't working well, and was upsetting my stomach.

My arm is pain free after 3 days (used twice a day for 4 hours a time).

The packaging is nice, comes with a neoprene fitted sleeve, an ace wrap, and the PEMF

Testimonials

pad.
I'd recommend to anyone seeking relief from pain.
jc

★★★★★this works great!!!!, October 28, 2009

By Edward Mckay "Shreddie" (Delaware)

Amazon Verified Purchase(What's this?)

This review is from: Actipatch Pain Therapy -Bioelectronics acti-patch Heel pain patch (Health and Beauty)

I use this patch every day on my ankle its helped me get back to skateboarding hard

I think everyone should get one!!!!

Other Testimonials:

Our daughter had to have nerve ablation done. The Doctor told her she would be in severe pain for several weeks. The first night was so bad she almost went to the ER. She called me and I asked if she had put on the back pain patch. She said no and did it immediately. She "never" was in severe pain after that. I have MGUS, a high IGM antibody and osteoarthritis, I use all the patches on different areas of my body for pain relief. THEY WORK, and I am so thankful for the developer for this product.

Kimberly Fitz

I had suffered from a knee injury because I fell onto a concrete floor at work. My left knee was inflamed, swollen and painful. I couldn't wear any uncomfortable shoes nor drive my car (which has manual transmission). The Actipatch was a huge relief for me because today I can wear any stylish shoe I want and the persistent pain is gone!

I'd like to extend to the makers of Actipatch a big "Thank you!"

Aimee Hall

"I have suffered with heel pain for several years. I have tried therapy, cortisone shots and surgery, nothing ever helped the pain. I tried the ActiPatch and was immediately relieved of the pain I have been living with for years. ActiPatch is an amazing device."

Cathy Clarke

"When I snapped my plantaris tendon I experienced more pain than any other time in my life. I applied ActiPatch to my leg in the early afternoon and by the end of the day my leg was feeling better. Within 2 days I was able to walk without a limp and within a week I felt great."

Tom Mulleady

Testimonials

"I had a knot in my upper shoulder that was causing me great pain, to the point where I could not turn around. I tried ibuprofen and other OTC pain relievers to no avail. I applied ActiPatch and 24 hours later the pain was gone!"

Patrick Haley

"I will probably wear ActiPatch on my left hip for the rest of my life because it gives me such relief! Sometimes after wearing one for a full week I am so improved I can stop for awhile... then if the pain comes back weeks later I can resume wearing it. ActiPatch is a very remarkable pain aid and I am amazed by its effectiveness."

Sheila McGuire
Encino, CA

"After years of being an aggressive athlete and now being in the bar business, I've started to develop several different aches and pains. With every ache that has started, I put a patch on it and within a few hours have felt relief! When I have worn the patch for the recommended time frame, I haven't had the pain again. The heel gel insoles have done wonders for me since I'm on my feet 6 days a week. I highly recommend the patches to anyone that has any pain and refer them to my friends and coworkers in the industry as the magic patches!"

Tara Kovatch
Hoboken, NJ

"I've had a "tennis elbow" due to a sprained neck, and couldn't get any relief. Well...I don't care what anyone says...my ActiPatch worn on my elbow has done the trick.... LOVE IT!!"

Dana Gordon

"After watching a ten to fifteen minute segment on the Dr. Oz show, dealing with pain relief from pulsed electro-magnetic therapy, I immediately ordered the ActiPatch, (back patch unit). For the last two months I have had significant pain relief on my right shoulder. I am currently on a waiting list for total shoulder joint replacement. After wearing the ActiPatch on my shoulder for approximately 3-4 days, (8 hours a day), my pain has been reduced by about 50-60% thus far. I recently postponed the shoulder replacement surgery, and continue to use the ActiPatch, hoping that I may be able to avoid the replacement surgery altogether."

Rich Vizzusi
Lincoln, CA

Testimonials

RecoveryRx Testimonials

"I have recently added RecoveryRx to my recovery protocols to help patients heal better after surgery. RecoveryRx works by driving out the swelling of the negative by-products from the damaged tissues. With less swelling, a decrease in pain occurs. RecoveryRx is wearable technology that is safe, easy to use, and low cost. RecoveryRx has shown to be effective in reducing pain in breast augmentation, abdominoplasty, blepharoplasty, nose and facelift surgeries."

Barry Eppley, MD, DMD
Plastic Surgeon
Indianapolis, Indiana

"The RecoveryRx has made a world of difference in post-op pain control in my patients. We apply the RecoveryRx to all abdominoplasty patients. The difference in pain control is amazing."

Kimberley B.C. Goh, MD, FACS
Myrtle Beach, SC

"When RecoveryRx is used, patients have much less post-op meds in the PACU."

Sandy Conley, RN

"I have noted that the patients who are using RecoveryRx for breast surgery report to have either no pain or only minimal pain in the post-op phase 1 and phase 2 areas of recovery."

Tara Reed, RN

"Patients who use RecoveryRx seem very comfortable and ask for less pain medication even through phase two recovery."

Darlene Stone, RN

Testimonials

"The remarkable thing is that the nurses who work in recovery can tell which patients are using the RecoveryRx and which are not, by the level of discomfort and the amount of pain medication that they have to administer."

David M. Whiteman, MD FRCS
Duluth, GA

"I use RecoveryRx on every facial procedure. It reduces my patients bruising and swelling by 50% following Blepharoplasty, Face Lifts, and Rhinoplasty. As a result of RecoveryRx, two weeks of standard surgical recovery has been reduced to 5-7 days."

Laurie Casas MD, FACS
Northwestern University
Feinberg School of Medicine

"For the first time in nearly 2 weeks, I was able to do leg presses without excruciating patellar tendinitis. I have been wearing the 3.5 sq RecoveryRx every night for about 10 days about 12 hours per night and there is significant healing. I haven't felt this good in nearly 3 years. RecoveryRx is a great product. I will continue wearing these pads forever if I have to."

- Keith Roberts

"I had surgery on October 8, 2007 and was given the opportunity to try your RecoveryRx for pain. There was virtually no pain during the time that I used them and experienced no side effects either. I would recommend RecoveryRx to anyone in need of relief from post surgery pain."

- Deborah Carello

Testimonials

Allay Testimonials

"I used to suffer from severe menstrual cramping, pain, and discomfort. I discovered Allay after years of investigating ways to alleviate my pain and the pain experienced by my patients. I prescribe Allay to my patients because I believe it is the most effective drug-free product on the market in relieving severe menstrual pain and discomfort."

Dr. Sheena Kong, M.D
Board Certified Internist
San Francisco, CA

'I have been bothered by severe menstrual cramping all my life and have used about everything available over-the-counter.....nothing really works well.....and it can be a week of misery. I tried the Allay patch and, while it did not eliminate all my discomfort, it made my typical week of misery much better. This is the best thing I have found yet and it doesn't involve taking any drugs!'

Charlene
Lafayette, Indiana

'The idea of wearing a patch to help my menstrual cramps initially seemed far-fetched. How could something on the outside work on the inside? But I trust Dr. Eppeley as my plastic surgeon and he suggested I give it a try....after all what did I have to lose and it wasn't a drug? To my surprise, I had the most comfortable week that I have had in months. I shall definitely use it again next month. It is easy to use and wear.'

Ronda
Columbus, Indiana

'The Allay device is a natural extension of the use of ActiPatch technology. ActiPatch has been very helpful in reducing discomfort from facial and body plastic surgery in my practice. Knowing the positive benefits of low frequency pulsed electromagnetic fields after invasive surgery, applying it to the problem of menstrual discomfort is a logical and no-risk extension of those potential benefits. It is easy to wear, well accepted by the patient, and has no downside. It is a non-drug anti-inflammatory therapy that is immediately reversible and affordable. While it will not eliminate all menstrual pain in every patient, it will clearly be of benefit for many women.'

Dr. Barry Eppeley

Testimonials

Plastic Surgeon
Indianapolis, Indiana

"On any given month, I typically spend anywhere from 8 – 12 hours in bed in extreme pain. The Allay Patch wasn't an immediate fix for me. After about 30 – 45 minutes, I could feel the patch starting to work, cramps starting to ease, and after about 2 hours, I was able to get up and get on with my day. I've used the patch twice with similar results after less than 2 hours, I was able to get up, move around, and be on with my day!"

- Junie Cleaver

"I suffered from miserable, monthly menstrual cramps. I'm talking stay home from school, writhe-around on the floor, moaning and crying suffering. I started using Allay and it was effective in lessening my cramps!"

- Kelly

"My periods were so bad I used to miss school. I used to take 900mg of ibuprofen multiple times a day to get rid of period pain. Now when I put on an Allay patch before the pain starts, the pain never comes! That's how I experienced Allay!"

- Alexis Callas

"For years I've been using Tylenol for my menstrual pain. Then I discovered [Allay]. I'm now really happy using this product instead. Thanks for developing this great product!"

- Anonymous

"I have become a strong advocate of holistic and herbal remedies, as I am so conscious of what I put into my body – and so do not use any chemical medicinal relief. As I suffer quite badly from menstrual pain, I did some research and found the Allay patch, which is a wonderful drug-free alternative that helps ease the pain. It contains a microchip that uses pulsed electromagnetic field (PEMF) therapy to stabilise the membrane of the uterus cells and stops the release of pain. I couldn't actually believe how effective it was, and it even reduces any sign of bloating too, which is an added bonus."

-Celebrity Sophie Anderton, United Kingdom

Testimonials

"My meds weren't providing me relief, so I decided to try Allay. Within an hour of applying the Allay patch, my pain went from an 8/10 to a 2/10."

- Connie Escullera, Washington, D.C.

"Over the last 10 years or so I developed several fibroids that cause heavy bleeding and severe menstrual cramps. I used to have to take at least a day off from work and lay in bed all day dealing with great pain. That was until I discovered the Allay Patch! Now at the first sign of cramps, I put the "magic patch" on and within 2 hours or less I'm back to my normal self again! I miss those days off from work, but I don't miss that unbearable pain!"

- Tara Kovatch, Hoboken, NJ

5.0 out of 5 stars **Saved me stress**, 24 May 2012

By [Bowler](#)

This review is from: Menstrual Pain Relief Therapy - Drug-Free & Clinically Proven (Misc.)

Brought this for my wife and she loves it and I do too :-). No more pain medication for her and Tylenol for my headache :-)