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STATE OF THE ART IN ELECTROMAGNETIC THERAPEUTICS: SOFT TISSUE APPLICATIONS.

Arthur A Pilla.

Bioelectrochemistry Laboratory, Department of Orthopaedics,
Mount Sinai School of Medicine, New York, NY 10029 USA.

INTRODUCTION

There is increasing use of pulsed electromagnetic fields (PEMF) as adjunctive therapy for a variety of musculoskeletal injuries. PEMF in current orthopaedic clinical practice has been employed to treat delayed and non-union fractures[1-5], rotator cuff tendinitis[6], spinal fusions[7] and avascular necrosis[8]. A clinically relevant response to the PEMF signals in current clinical use is generally not immediate, requiring daily treatment for several months in the case of non-union fractures (although experimental signals now exist which elicit significantly faster response[3]). In contrast, clinically effective electromagnetic treatment of sprains, strains, contusions and other soft tissue injuries such as wounds, would require a physiologically meaningful response in hours or days. Until recently, application of EMF signals to other pathologies such as soft tissue and musculoskeletal injuries and post-surgical, post-traumatic and chronic wounds has been sparse. This review summarizes the present status of the use of low or non-thermal pulsed radio frequency (PRF) signals for such pathologies.

PEMF AND PRF SIGNALS

The group of most commonly used electromagnetic signals for therapeutic applications are pulse type (PEMF) signals having maximum spectral density in the low frequency range[3]. PEMF signals commonly consist of repetitive bursts of symmetric or asymmetric pulses, having durations of several microseconds to several milliseconds[3]. Maximum induced electric fields from PEMF signals are in the mV/cm range at frequencies below 5 kHz. In contrast, a PRF signal consists of repetitive bursts of sinusoidal waves in the short wave band, usually in the 13-40 MHz range[9]. Non or low thermal PRF signals in current clinical use consist of 10-100μs bursts of (usually) a 27.12 MHz sinusoidal wave carrier repeating at 10-1000/sec. This signal induces peak electric fields in the V/cm range at 27.12 MHz, a significantly higher frequency than that at which PEMF waveforms induce mV/cm electric fields. Spectral analysis of both signals reveals that the PRF signal has components in the MHz range of significantly higher amplitude than those for the PEMF signal. In addition, since the PRF signal is a repetitive pulse burst it has low frequency components which are remarkably near the amplitude components in the same range for the PEMF signal.

The PRF signal, thus, has frequency components which have sufficient amplitude to elicit a possible bioeffect over a significantly broader band than those for PEMF signals, allowing it to couple to targets having a wider array of kinetics. This is illustrated in figure 1, left, wherein the frequency response and signal to thermal noise ratio (SNR) of an ion binding pathway at a macromolecule to both PRF and PEMF signals is compared. For this example the peak induced magnetic field was 0.2G for a PRF signal consisting of a 500μs burst of a 27.12 MHz sinusoidal carrier repeating at 1/sec, and 20G for a clinical PEMF signal consisting of a 5msec burst of 200/20μs asymmetrical pulses repeating at 15/sec. The frequency characteristics for the ion binding pathway were derived from the known kinetics[10] and EMF response[11,12] of

Ca^{2+} binding to calmodulin in a cell-free myosin phosphorylation assay. The efficiency of signal coupling to this pathway may be judged by examining SNR frequency response (figure 1, left) which clearly indicates that a measurable bioeffect (SNR > 0.1) could be observed with both PRF and PEMF signals, i.e., the induced voltage is detectable by the targets throughout the useable frequency range. Experimental evidence for a PRF effect using the signal characteristics employed for figure 1 has been reported[12]. Note that SNR analysis, which has been discussed in detail elsewhere[13] is substantially different if the target consists of cells in gap junction contact and a change (perceivable within thermal noise, SNR > 10^{-1}) in transmembrane voltage is desired. Figure 1, right, shows the same PRF and PEMF signals also have sufficient amplitude components in the low frequency range to expect a bioeffect for a cell array target such as repairing tissue. Remarkably, the PRF signal can couple as efficiently as the PEMF signal to the cell array which has the frequency characteristics of a low pass filter. There have been many reported applications of PEMF waveforms for bone repair[1,2,5,7]. The use of a PRF signal having parameters identical to that analyzed here has only recently been reported[12]. It is of interest to note the PEMF waveform must be used at least 4 hours daily, whereas the PRF signal requires only 30 minutes daily. This may be related to the larger frequency range over which the PRF waveform has components of sufficient amplitude to achieve SNR levels at which observable bioeffects may be possible.

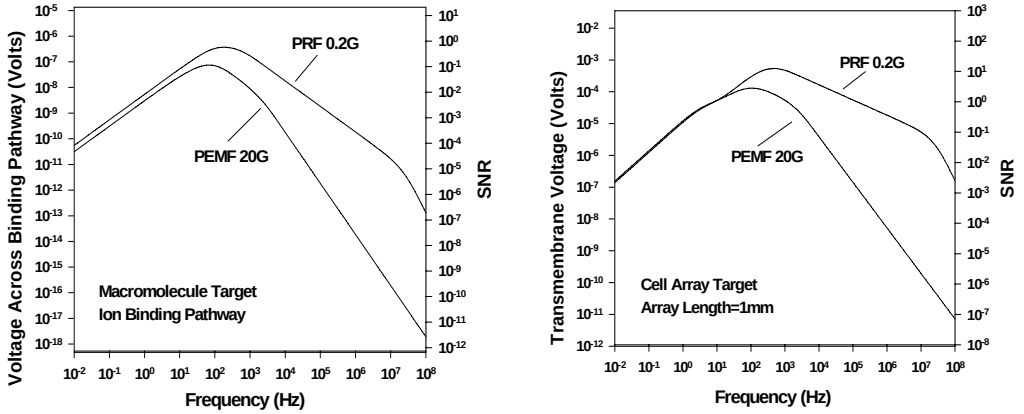

Figure 1: Comparison of frequency response and SNR to a PRF signal consisting of a 65µs burst of a 27.12 MHz carrier repeating at 600/sec and a PEMF signal consisting of a 5 ms burst of asymmetrical pulses (200/20µs) repeating at 15/sec for an ion binding pathway at a macromolecule, **Left**, and at a cell array, **Right.** Both signals have components of sufficient amplitude in the frequency range of the target and could, therefore, be bioeffective (SNR > 10^{-1}) at both the tissue and molecular level.

CLINICAL APPLICATIONS OF PRF SIGNALS

Non or low thermal PRF signals were originally employed for the treatment of infections in the pre-antibiotic era[14]. Since this original work, the most prevalent and effective clinical applications of PRF signals are related to the reduction of pain and edema. Double-blind clinical studies have been reported for chronic wound repair[15], acute ankle sprains[17], and acute whiplash injuries[18,19]. The tissue inflammation that accompanies the majority of traumatic and chronic injuries is essential to the healing process, however the body often over-responds and the resulting edema causes delayed healing and pain and possibly long term disability[20]. For soft tissue and musculoskeletal injuries and post-surgical, post-traumatic and chronic wounds, reduction of edema is thus a major therapeutic goal to accelerate healing. As a example of the use of PRF therapy to accelerate healing from an acute injury, results from a double blind clinical trial on lateral ankle sprains will be summarized here. The ankle sprain serves as a good model of soft-tissue inflammation as it typically exhibits edema and pain with disability. This clinical study determined if PRF treatment, in addition to conventional treatment (rest, ice, compression, and elevation) could accelerate the rate of edema reduction. The effect of PRF therapy on edema volume was determined. PRF therapy was provided in a double-blind, placebo-controlled fashion, in addition to standard treatment (rest, elevation, compression, cryotherapy), for Grades I and II lateral ankle sprains. This prospective study was conducted at 14 clinical sites within the U.S. (n = 13) and Canada (n = 1) over an 18 month period.

The Clinical Model: Lateral ankle sprains are classified into three grades. Grade I injuries are associated with perceived and palpable pain of the lateral ligamentous complex, minimal swelling and little instability when compared to the contralateral side. Grade II injuries are of moderate severity and involve greater ligamentous disruption. Grade II sprains are noted for marked swelling, pain and abnormal joint laxity. Grade III lateral ankle sprains represent the most morbid sprains with significant pain, swelling and joint

instability. In addition, hemarthrosis and avulsion fractures may be present. Ankle injuries of moderate severity serve as excellent models for the evaluation of edema reduction using physical and pharmacological agents. Swelling in the lower limb in animal and human studies has been used to evaluate clinical efficacy of numerous interventions. Clinical evaluations of anti-inflammatory interventions requiring precise measurement of swelling volume are frequently performed using the foot and ankle.

Methods: Patients who experienced a lateral ankle sprain (Grade I or II) and could receive the first PRF treatment within 48 hours were eligible for participation in this study. Informed consent was obtained. Patients enrolled were randomly divided into treatment (PRF) and sham treatment (control) groups. Both the patient and therapist were blinded to treatment group. Patients received a single 30 minute treatment on Day 1 and Day 2 after study entry. Swelling was measured before and after each treatment session and on Day 3. Edema volume of the injured ankle (ml) was measured by the water displacement method both before and after treatment. All clinical sites were provided with one active and one sham PRF unit and the code was broken at the completion of the study. All patients in the active treatment group were treated with a PRF signal in current clinical use, consisting of a 65μs burst of 27.12 MHz sinusoidal waves (in the short wave band) repeating at 600/sec. The peak magnetic field in tissue was approximately 2G corresponding to a peak induced electric field of 1 V/cm and peak current density of 1 mA/cm^2 in a typical ankle target, similar to that delivered by high voltage galvanic stimulators (HVGS) clinically utilized for edema reduction and wound healing[34,35]. PRF dose was monitored via magnetic field measurements using a calibrated probe[36,37]. All data were evaluated using a one-tailed unpaired Student's t test, since PRF treatment was expected to have a unidirectional effect on edema (decrease, as opposed to increase, in this study). The analysis of variance F test confirmed there were no significant difference in the variances for all comparisons. The Kolgomorov-Smirnov test confirmed all data sets were normally distributed. Significance was accepted for $P \leq 0.05$.

Results: This study recruited 439 subjects at fourteen centers. Of this total, 395 patients completed the protocol, 193 in the control and 202 in the active groups, respectively. There were no reports of any adverse events. The difference of Day 3 to Day 1 edema volume measurements, as well as the rate of edema volume change over the same period, were evaluated for all patients, and the means for the active and control groups were compared. Edema decrease in the PRF treated group (-12.0±4.1 ml) was approximately 7x greater than that in the control (sham treated) group (-1.6±3.6 ml), P=.03 (see figure 2, left). These results suggest edema was basically unchanged in the control group, whereas a significant reduction of edema volume was observed for the group exposed to PRF therapy over the treatment and observation period. The mean rate of edema decrease (indicative of time in inflammatory phase) for this period in the PRF treated group (-5.8±2.1 ml/day) was nearly 5x that in the sham treated group (-1.2±1.8 ml/day), P<0.05 (see figure 2, right). This again suggests the rate of edema change was not significantly different from zero in the control group, while a large edema decrease could be expected in the active group.

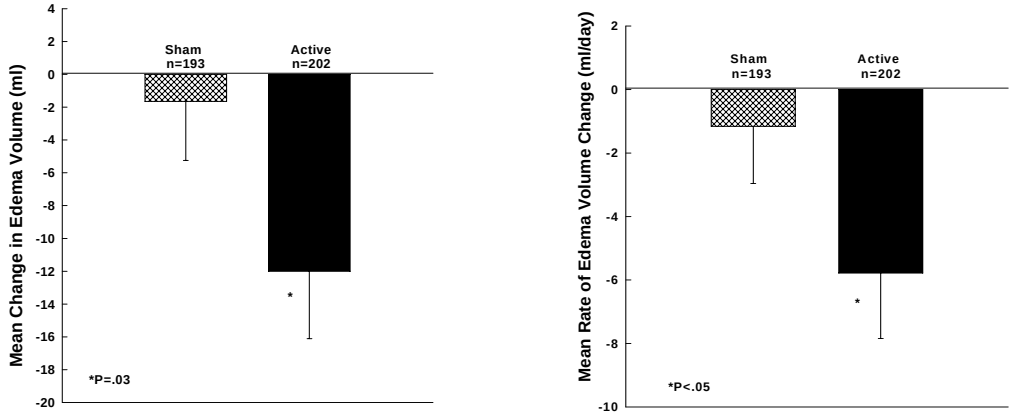

Figure 2: Left, Effect of PRF therapy on edema volume from grades I and II lateral ankle sprains for all subjects completing the study. Mean edema decrease from Day 1 to Day 3 post study entry in the PRF treated group was >7x that in the sham treated group. **Right,** Effect of PRF therapy on the rate of edema decrease in grades I and II lateral ankle sprains for all subjects completing the study. The mean rate of edema decrease was nearly 5x greater in the PRF treated group vs that in the sham treated group, suggesting less time in inflammatory phase leading to increased rate of healing..

DISCUSSION AND CONCLUSIONS

The results presented above, as well as those reported elsewhere[12], clearly demonstrate PRF signals can have significant bioeffects if the waveform is constructed such that sufficient SNR can be obtained for the target in question. The PRF waveforms in current clinical practice, while not efficiently constructed, induce electric fields having sufficient amplitude components at appropriate frequencies for detection by cell

array targets (tissues). In contrast, PEMF signals appear to be useful only for cell arrays, but not for single cell or molecular size targets. It is also important to note that a physiological response to PRF in the case of acute injuries is often reported during or immediately after treatment compared to the significantly slower response customary for the PEMF signals utilized for bone repair. Although the exact mechanism for PRF bioeffects is not completely understood, it is certain that the broader frequency spectrum of PRF signals allows efficient coupling to the kinetics of a multitude of target pathways. For example, it has recently been reported that the voltage changes induced by PRF at binding sites in macromolecules are sufficient to affect ion binding kinetics with resultant modulation of biochemical cascades relevant to the inflammatory stages of tissue repair[16]. In the case of clinical applications to acute pathologies, such as ankle sprains as presented above, the effective broad frequency spectrum of PRF signals may: (i) reduce local bradykinin release which is known to increase edema formation[21]; (ii) increase epinepherine release which may dilate blood vessels; or (iii) modulate the release of growth factors involved in tissue repair[21]. Affecting any or all of these effects may reduce healing time in acute injuries.

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