

A Clinical Study to Evaluate the Magnopro Device in the Management of Myalgia and Arthralgia of the Knee

Sponsored by: Body Fields USA Inc.
1645 South River Road, Suite 5
Des Plaines, IL 60018

Institutional Review Board: Texas Applied Biomedical Services
Houston, Texas

Protocol Date: July 20, 2006

Revised Date: October 03, 2006

Final Report Date: October 14, 2007

EXECUTIVE SUMMARY

The study objectives were to evaluate the safety, tolerance and efficacy of the Magnopro device on pain intensity in male and female adult subjects age 18 years or older with acute and/or chronic knee pain. The subject population studied included those subjects with joint and soft tissue pain due to injuries and surgeries, chronic sprains and strains, bursitis, nerve injuries, non-specific neuritis or neuralgia and other types of pain, including pain resulting from arthritis.

The statistical results are excellent regarding the effect of the Magnopro on knee pain as measured with the Visual Analog Scale (VAS). The statistical significance achieved in lowering chronic knee pain is $p < 0.001$. Typically, a p value of 0.05 or less is accepted as statistically significant. The effects of the Magnopro treatment protocol on the physiological parameters that were measured were not statistically significant.

There were 20 subjects completing the study. Unfortunately, many subjects had to drop out due to the intense treatment schedule that interfered with their travel and family schedules. The high dropout rate significantly slowed down the project completion.

I. SPECIFIC AIMS

The study objectives were to evaluate the safety, tolerance and efficacy of the Magnopro device, a non heat producing pulsed weak electromagnetic field (EMF) generator, on pain intensity in male and female adult subjects age 18 years or older with acute and/or chronic knee pain. The subject population studied included those subjects with joint and soft tissue pain due to injuries and surgeries, chronic sprains and strains, bursitis, nerve injuries, non-specific neuritis or neuralgia and other types of pain, including pain resulting from arthritis. The study explicitly excluded pain from any and all forms of cancer.

II. BACKGROUND AND RATIONALE

A. Pain Remains a Major Medical Problem

Pain is one of the commonest symptoms in medicine and it is the prime cause of one third of all first consultations (Bowsher 1987). While cure of the causative condition usually relieves the pain, it may on the other hand continue beyond its diagnostic usefulness, either because the disease is itself incurable, or because irreversible anatomical changes lead to continuing noxious stimulation (Bowsher 1987).

Acute and chronic pain control is now a major concern especially with population ageing and associated pain of the chronic degenerative conditions of the elderly such as osteoarthritis, post-herpetic neuralgias, trigeminal neuralgia, reflex sympathetic dystrophy, and malignant diseases. Thus in an ageing population the medical, social, and economic consequences of chronic pain may be expected to increase (Bowsher 1987).

The primary symptom in most patients with disorders affecting the soft tissue is pain. In many patients, daily activities are limited as pain causes a restriction of the range of movements. Causes of soft tissue pain can be depicted as musculoskeletal, neurologic, vascular, referred visceral-somatic or articular (Cailliet, 1991).

Since the beginning of the present century, theories of pain mechanism have evolved from specificity and summation models to the popular gate control theory. This latter pain theory, proposed by Melzack/Wall/Casey (Wall and Melzack, 1989) has become the most important development in the field of pain management. More and more discoveries in recent years show that pain perception is no longer a straight forward afferent transmission of pain signal. It is a complex mechanism involving modulation coming from both peripheral and central nervous system. In the chronic pain state, pain signal generation can actually in the central nervous system without peripheral noxious stimulation.

Anatomically, there are numerous ascending excitatory and descending inhibitory pathways in pain signal transmission. Centralization (cephalad relocation in the central nervous system) of the pain signal generators occur spontaneously or after these neural pathways are interrupted, leading to totally unexpected pain syndromes. Advanced reflex sympathetic dystrophy, deafferentation pain and phantom pain phenomenon are just a few examples (Adams, et al 1997).

Traditionally, we believe that pain is an important biological reaction of defense and a fortunate warning to put us on our guard against diseases. Although this may be true in disease states such as appendicitis, fracture and angina, it does not explain the unnecessary pain in conditions such as migraine, post-therapeutic neuralgia and pain in labor and delivery. Scientific evidence shows that acute persistent pain eventually sensitizes wide dynamic neurons in the dorsal horn of the spinal cord, the wind-up phenomenon, constituting the basis of developing chronic pain syndromes (Kristensen, 1992). Persistent and excessive pain has no biological function. It is actually harmful to our well being. Therefore, pain needs to be treated as early and as completely as possible, not to be left alone (Adams, et al 1997).

Commonly, pain syndromes present with different mixtures of types. In acute pain (predominantly nociceptive), visceral, somatic and referred mechanisms play important roles in the pain perception. In chronic pain (frequently non-nociceptive), neuropathic and psychogenic mechanisms prevail, resulting in protracted suffering and disability both physically and mentally.

We used to believe that destruction of the pathways of pain transmission would alleviate the pain. This has proven to be wrong. Due to the plasticity of our nervous system, the pain relief achieved by neuroablation is most of the time short lived. In pain management, modulation of pain signal transmission is a far better choice than destruction.

The impact of any successful clinical trial in the treatment of acute and chronic pain using therapeutic means that are conservative and with no side effects is quite significant. We know today that the most frequent aches are back pain and headache, followed by the neck pain, toothache and stomach ache. For instance, back pain is widespread condition, especially in the industrially developed countries, where it has become almost an epidemic. 30-40% of population between 10 and 65 years of age visit their physician at least once a month due to back pain (Simunovic, 2000).

Whatever pain management will be applied, it is clear that the pain, especially its chronic form, is a complex process, which deeply affects a person's life, forcing some alterations in professional, private, social and other aspects of everyday activities.

The American College of Rheumatology (ACR) defines chronic musculoskeletal complaints as those lasting longer than six weeks (ACR, 1996).

Therapies used to treat soft tissue pain include non-steroidal anti-inflammatory drugs (NSAID), steroid injections, therapeutic ultrasound, and physical therapy including passive and active exercise, moist heat and massage. In addition to these therapies, transcutaneous electrical nerve stimulation (TENS) has also been used. Early reports of applying electrical current to treat pain date back before 1800 (Ersek, 1981).

Treatment of pain remains a major medical problem, especially in cases where the etiology is unidentified. Pain associated with any injury, ailment or medical conditions are sometimes difficult to treat. Many of the current modes of pain therapy such as mild analgesics or topical creams may be ineffective, or in the case of

antidepressants may have undesirable side effects, or may be invasive (e.g. nerve blocks).

B. Pain Reduction

Time-varying magnetic fields have successfully been used for pain control associated with rotator cuff tendinitis, multiple sclerosis, carpal tunnel syndrome, and periarthritis (Battisti et al, 1998; Lecaire et al, 1991). For example, an improvement was observed in 93% of patients suffering carpal tunnel pain and 83% in rotator cuff tendinitis. Time-varying magnetic fields were also used for treatment of migraine, chronic pelvic pain, neck pain, and whiplash injuries (Rosch et al, 2004).

It is necessary to understand the mechanism of pain transmission to understand how pain blocking with PEMF can take place. Pain is transmitted along nerve cells as an electric signal. This encounters synaptic gaps at intervals. The pain signals are transmitted across the synaptic cleft in the form of a biochemical transport. During quiescent times the cells possess a small charge of about -70mV between the inner and outer membranes. When a pain signal arrives it depolarizes the nociceptive cell raising the cell membrane potential to $+30\text{mV}$. This opens channels in the cell membrane allowing an exchange of Ca^{++} and K^+ ions which trigger exocytosis of neurotransmitters via synaptic vesicles. These neurotransmitters diffuse into the synaptic gap. Once this has occurred the cell depolarizes to its previous level of -70mV (Adams, et al 1997).

Research by Warnke established that the application of pulsed magnetic fields have an effect on the quiescent potential of the neuronal synaptic membrane (Warnke, 1983; Warnke, et al 1997). It suggested that the effect is to lower the potential to a hyper polarized level of -90mV . When a pain signal is received it then has to raise the potential again in order to fire an action potential via neurotransmitters, but only achieves to raise the cell membrane potential to approximately $+10\text{mV}$. Since this is well below the threshold necessary to release the neurotransmitters into the synaptic cleft, the pain signal is effectively blocked (Adams, et al, 1997).

C. Brief Background on the Magnopro Device

Common magnetic measuring devices for the human body include magnetic resonance imaging (MRI) and the Super Conducting Quantum Interference Device (SQUID), which have been developed to measure weak magnetic signals throughout the body. The Magnopro is a device for applying a therapeutic pulsed electromagnetic field to biological entities. The device is comprised of a signal generation unit for generating an electrical magnetic treatment signal having a plurality of superimposed frequency components of approximately 300Hz, 600Hz, 800Hz and 1,000Hz (Basic Signal) and between 2–32Hz (User Signal). An induction coil mat is connected to the signal generation unit and generates a pulsed magnetic field in accordance with the electrical signal.

The Magnopro is a special inductor which produces short duration, fast rising, bipolar magnetic pulses which induce an alternating electrical field of low peak (instant) voltage which produces low peak (instant) electric current.. Bioenergy is the activation of the internal degrees of molecules of biomatter. Bioenergy as an activation of internal degrees of molecules is distinct from heat energy which is the

activation mainly of the external degrees as explained further in Section 3. The main difference of bioenergy to heat energy is bioenergy appears to cause synthesis or composition leading to complex structures of bio-molecules. On the contrary, heat causes decomposition or destruction of complex bio-molecules –the diathermic effect (Nelson P, 2003; Prasad P, 2003).

D. Effect on General Injuries

Bone repair, neurotransmission intensification and DNA synthesis are all linked to the same causal modality, namely pulsed, low intensity magnetic fields (Liboff et al, 1984; Rosch et al, 2004). Proteins are fundamentally conductors of electricity. Proteins are subject to electrophoresis in strong fields displayed throughout diagnostic manipulations. Since DNA is subject to mechanical influence by messenger RNA and RNA is subject to influence by encoded proteins, the flow of information to and from genes may be linked to electromagnetic fields (Einstein, 1977; Goodman et al, 1983).

Since magnetic fields interact with moving charges, and recent studies(Dandliker et al, 1997) show that DNA can conduct electrons along the stacked bases within the DNA double helix, it has been suggested that weak electromagnetic fields initiate transcription of mRNA by accelerating electrons moving within DNA (McLean et al, 2003).

Nobel Laureate Albert Szent-Gyorgyi established that structured proteins behave like solid-state semiconductors or rectifiers (Szent-Gyorgyi, 1976). Cell membranes can rectify an induced voltage and this rectifying property of cell membranes can cause changes in the ion concentration of the inner and outer surfaces of the cell membrane in such a way as to increase the transmembrane potential and effectively stimulate the activity of the Na/K pump. Cell health is directly affected by the health of the Na/K pump, which is directly proportional to the transmembrane potential.

Enhanced spinal cord regeneration in Lamprey by applied electric fields has been demonstrated utilizing 10 microamps. In Rana and Xenopus limb regeneration and increased nerve growth was due to direct artificially imposed current of 200 nanoamps (Borgens et al, 1981).

In terms of common injuries, bruising and others PEMF has been researched thoroughly (Rosch et al, 2004). The effects on damaged tissue can be explained with regard to the cellular structure. Healthy cells in tissue have a membrane potential difference between the inner and outer membrane. This potential causes a steady flow of ions through the membrane pores. When the cell is damaged the membrane potential is raised and a larger than normal sodium inflow occurs. The net effect is that interstitial fluid is attracted to the area of damage and therefore swelling and edema occur.

The application of PEMF to damaged cells has been shown to help accelerate the re-establishing of normal cell potentials and hence increase the rate of healing and reduction in swelling (Rosch and Markov, 2004).

E. What is Pulsed Electromagnetic Field (PEMF) Therapy?

An electromagnetic field is a combination of magnetic field and electric field. The basic physics suggest that when the amplitude of the magnetic field changes, an electric field is generated and vice versa. Also, any time-varying magnetic field is accompanied with a time-varying electric field (Lorrain, 2000).

Permanent or static magnets deliver to the human body a magnetic field only. If a magnetic field is generated via a sinusoidal wave generator, one should expect the effect to be a result of both magnetic and electric field components. This is even more important in a case when superficial tissues are exposed to magnetic field treatment. While the magnetic field penetrates the biological tissues, the surface of the human body acts as a barrier for electric field and the incident electric field is transferred in an electric current over the body surface.

All the cells of the body have a weak, natural electric current flowing through them. The currents are caused by electrically charged particles in the cells called ions. Ions affect the metabolism, or the work of the cell. PEMF is a method of applying a magnetic field to the cell which converts the magnetic field into a weak electrical current, influencing the interaction of the ions and the flow of nutrients in the cell. Enhanced circulation and nutrient exchange can speed the healing process and reduce down time.

F. Explanation of the Effects of the Magnopro

The principles by which the Magnopro work are several, beginning with the sub-atomic level.

As the pulses expand and collapse through the tissue the protein molecules such as cytochromes in the cell mitochondria, gain electrons and therefore receive and store energy. Due to the low amplitudes generated by the Magnopro, the energy is not high enough in the tissues to create heat, or for the cell atoms to vibrate and create a thermal change, or for an electron to jump to higher orbits and express heat as it returns to its natural orbit. There is energy only for the actual spin on the electron to be increased, and this becomes stored energy. The stored energy is used by the cell's mitochondria to produce the ATP molecules and therefore able to express its genotype.

Studies have shown that biological processes that require a catalyst will take place with less catalyst when the area has been pulsed. Next level up, from the standpoint of quantum mechanics, the electron in shifting positions around an atomic nucleus generates a specific energy emission of magnetic resonance. The magnetic resonance field frequency of body tissue (and organs) is a product of the individual atomic, molecular, and cellular frequencies that make up that organ.

From the perspective of biophysics, the initial step of pain development (occurring from damaged tissue) is considered to be “disorder” of the magnetic resonance of a normal atom. When this disorder of magnetic resonance occurs the magnetic resonance of regular electrons at the atomic level exhibits a change (phase shift) which breaks and disturbs the once orderly communication pathway that is usually transmitted from atom to molecule, molecule to cell, cell to tissue, and tissue to organ. The pulsed fields of the Magnopro provide sufficient energy to restore this

imbalance of the magnetic resonance as the atom is re-energized to a level that existed before the damage occurred. The stored energy in the faster turning electron is drawn out to effectively balance the disruption of the packet of energy that caused the phase shift, and allows harmony to return to the order of the atom.

III. DESCRIPTION AND OPERATION OF DEVICE

A. Device Description.

The Magnopro (Figures 2 and 3) is a patented advanced electromagnetic device that produces unique bio-energetic magnetic field pulses characterized as having a fast rise time and short duration (US patent 10/219984).

The Magnopro is a special inductor which produces short duration, fast rising, bipolar magnetic pulses which induce an alternating electrical field of very low peak amplitude voltage which produces low peak (instant) electric current. Bioenergy is the activation of the internal degrees of molecules of biomatter. Bioenergy as an activation of internal degrees of molecules is distinct from heat energy which is the activation mainly of the external degrees. The main difference of bioenergy to heat energy is bioenergy appears to cause synthesis or composition leading to complex structures of bio-molecules. On the contrary, heat causes decomposition or destruction of complex bio-molecules – the diathermic effect (Nelson P, 2003; Prasad P, 2003).

A very brief understanding of the effects of the Magnopro at the atomic level requires a basic understanding of quantum mechanics and it is provided here. The vibrational states of a molecule are obtained by solving the vibrational Schrodinger equation of a molecule. A diatomic molecule, which only involves one vibrational degree of freedom (stretching of the bond), would provide a simple description (Atkins et al, 2002). Quantum mechanical considerations show that for the electronic excitation to the same orbital state of a particular molecule, the energy of an excited triplet state (say T₁ state in Figure 1) is lower that of its corresponding singlet state (S₁ in this case as depicted in Figure 1). The possibilities for the fate of an excitation to a higher singlet S₂ manifold are described below.

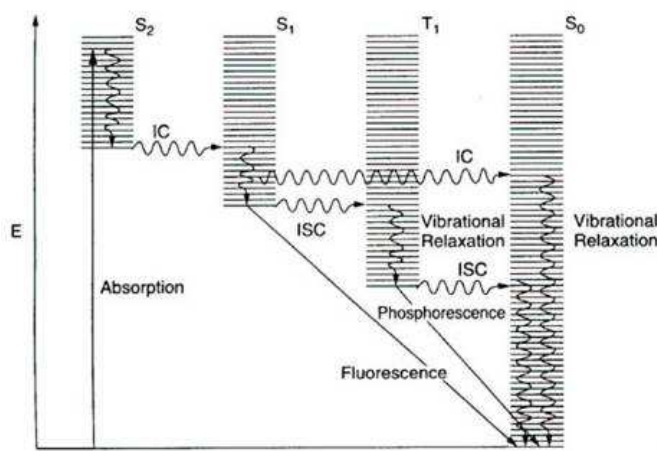


Figure 1. The Fate of An Electronic Excited State

The horizontal closely spaced lines in Figure 1 represent the vibrationa levels. In biomolecules the nonradiative crossing from the state S2 to S1 is generally the dominant mechanism. This crossing between two electronic states of the same spin multiplicity (such as from S2 to S1) is called internal conversion (IC) (Atkins et al, 2002). The IC process is then followed by a rapid vibrational relaxation (decrease) where the excess vibrayional energy is dissipated into heat, the molecule now ending up at the owest, zero-point vibrational level of the S1 electronic state. From here, it can return to the ground electronic state S0 by emitting a photon (radiatively). The Magnopro's time-varying EMF apparently affects electronic states via the intercrossing system (ISC), which is an excitation from state Si to Ti, where Ti is the corresponding triplet state (2 electrones are unpaired). The ISC type of crossing is heavily affected by the spin-orbit coupling, which relaxes the spin property by mixing with an orbital character (Szent-Gyorgyi A, 1976; Atkins et al, 2002). The ISC type of crossing leads to phosphorescence rather than fluorescence with radically different heat properties. Heavy metals, molecular oxygen (having a triplet ground state), paramagnetic molecules such as hemoglobin, and heavy atoms such as iodine increase the intersystem crossing rate (Prasad, 2003).

Regarding the gross physical characteristics of the Magnopro device, the main subsystems are the treatment mat and the control console (Figures 2 & 3).



Figure 2. The Magnopro Device Components



Figure 3. The Magnopro Control Console

B. Principles of Operation

Magnetic fields can penetrate practically any object, being very difficult to shield, and hence harmlessly penetrate the tissues and organs of the subject's body. There, by the phenomenon of Faraday induction, these oscillating magnetic fields induce a secondary weak electrical field that generates microcurrents in complete safety to the subject and operator. Since the maximum amplitude generated by the Magnopro is 1.75 gauss, no unsafe or ionizing radiation is generated by the device (See Risk Analysis section). These microcurrents have frequencies and wave characteristics identical with those of the electrical current discharge in the treatment mat. These induced electrical fields and currents carry energy to the cellular level and may increase the natural cellular activity with beneficial results. No electricity is transferred from the machine to the subject. The microcurrents are generated in the subject's tissues by a natural process of electromagnetic induction.

The Magnopro achieves its therapeutic effects by generating high frequency with very low amplitude electromagnetic pulses (less than 2 gauss) and with short duration (microseconds).

The Magnopro is a device for applying a therapeutic Pulsed Electric Magnetic field to biological entities. The apparatus is comprised of a signal generation unit for generating an electrical magnetic treatment signal having a plurality of superimposed frequency components of approximately 300Hz, 600Hz, 800Hz and 1,000Hz (Basic Signal) and between 2–32Hz (User Signal). An induction coil mat is connected to

the signal generation unit and generates a pulsed magnetic field in accordance with the electrical signal.

The fundamental or Basic frequency components discussed above are primarily responsible for initiating the biochemical processes within the body, for increasing cell membrane permeability and re-establishing normal potentials to damaged cells. In particular, these high frequency components (300-600-800-1,000Hz) are primarily responsible for providing an improved calcium cascade effect within the cells, where Ca^{++} ions penetrate cell membranes. These high frequency signals alone can provide beneficial treatment effects.

Further in each treatment program, a range of particular low frequencies is added, in the range from 3 to 32 Hz. These frequencies are chosen in accordance with a desired treatment mode of operation.

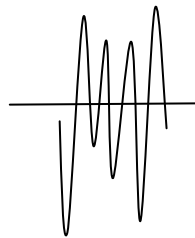


Figure 4. Basic signal 300 – 400 – 600 – 1,000Hz

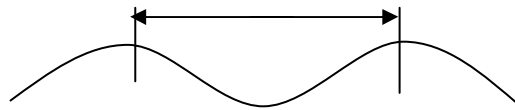


Figure 5. Low frequency from 2 – 32Hz

The above 2 separate waveforms are modulated in one useable waveform that is changing throughout the treatment as depicted in Figure 6.

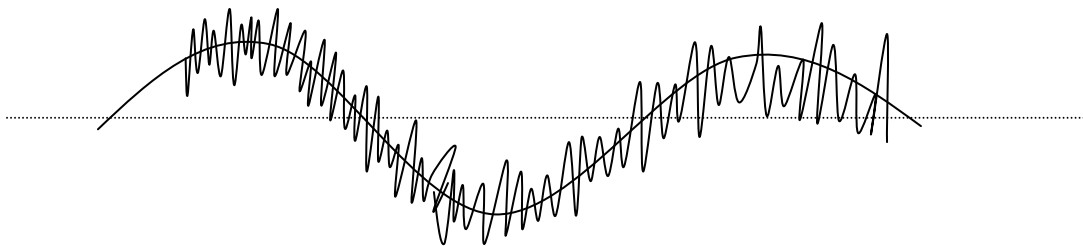


Figure 6. Combined waveforms generated by the Magnopro

The subject will follow the steps listed below for each treatment session. Figure 7 illustrates a subject using the Magnopro.

1. Turn on the power (switch located at the back of the control console; Figure 3)
2. Choose the program number by pressing button 1, 2, or 4 as per schedule
3. Choose time setting of 10, 15, or 20 minutes as required by protocol
4. Choose Intensity setting of 6 for all treatment sessions
5. Lie down or sit using a flat bed or recliner on the Magnopro Mat and place its pillow accessory over the anterior aspect of the affected knee
6. Push the Start button
7. The device will automatically stop after the selected time has elapsed. Turn OFF the power to the control console (switch located at the back of the control console; Figure 3).



Figure 7. Patient Using the Magnopro Mat

IV. RISK ANALYSIS

The Magnopro device produces maximum pulse amplitudes of less than 2 gauss, which is about 500 times less than a common static magnet used as note holders on refrigerators in most kitchens in the USA. (See table below)

| Magnopro | Intensity at maximum level | Intensity at maximum level |
|----------------|----------------------------|----------------------------|
| Programs 1 & 3 | 26 μ T | 0.26 gauss |
| Programs 2 & 5 | 16 μ T | 0.16 gauss |
| Program 4 | 175 μ T | 1.75 gauss |

μ T = Micro Tesla
1 Gauss = 100 μ T

The study sponsor, Body Fields Inc., has determined that the Magnopro device is a Non-Significant Risk device based on the following factors:

- The maximum amplitude generated is 1.75 gauss
- The most recent reports by researchers from the Neuromagnetics Division, Department of Neurology at Vanderbilt University Medical Center on the potential negative effects of pulsed EMF state that no teratogenic or cytogenic effects were found on field

exposures under 100 gauss (McLean, Engstrom, Holcomb, 2003). Cytogenic effects were demonstrated at flux levels higher than 10,000 gauss.

- Franco Bistolfi, in his book *Magnetic Fields in Medicine*, lists numerous studies that have been published on the beneficial effects of low amplitude (under 10 gauss) pulsed EMF (Bistolfi, 2001).

A. PEMF Effects in Non-Union Fractures and in Soft Tissues

In the mid-1800s, electric stimulation was the method of choice for slow-healing bone fractures (Lente, 1859). Direct current was passed through needles inserted directly into the fracture gap. The method was successful for bone fractures but soon abused by being applied to more and more human ailments, from cancer to colds, contributing to the backlash that led to the abolition of all electrotherapies (Rosch et al, 2004). Later on the realization that the microcurrents could be induced to flow in the fracture site noninvasively by magnetic induction with PEMF led to new device developments and later approval by the FDA in 1979. By 1982, Bassett was able to report an overall success rate at Columbia Presbyterian Medical Center in New York of 81%. Bassett stated that PEMF was used in the treatment of more than 300,000 un-united fractures, with no untoward events or hazards observed (Bassett et al, 1982).

After decades of clinical success with the use of PEMF for bone, attention turned naturally to injuries of soft tissue, such as nerve, muscle, and tendon and the pain associated with those injuries. A summary of the clinical results are provided by Siskin and Walker (Siskin et al, 1995). They observed no adverse effects reported and the following positive effects:

- Enhanced capillary formation
- Decreased necrosis
- Diminished pain
- Faster functional recovery
- Reduction in depth, area, and pain in skin wounds
- Reduced muscle loss after ligament surgery
- Increased tensile strength in ligaments
- Acceleration of nerve regeneration and functional recovery.

B. Precautions

Provided that the precautions listed below are heeded, there should be no significant risk to a subject undergoing Magnopro therapy.

Pacemakers

As with all EMF generators, the device should not be operated within four feet of an individual with a cardiac pacemaker or other bio-electronic device.

Water spills

As with all electrical appliances, contact with water or conducting liquids should be avoided. If a water or liquid spill should occur on the treatment mat or control console, the machine should be immediately switched off and disconnected from the mains power until the area is completely dry.

Divestiture of metal objects and electronic devices

The subject must divest themselves of all metal objects before treatment, including watches, jewelry, keys, credit cards, and any metallic pocket contents. Electronic beepers, calculators, mobile phones, tape recorders, electronically sensitive keys, remote control devices, and credit cards with magnetic strips should be kept at least three feet from the mat during operation.

C. Contraindications for Special Medical Conditions.

Blood pressure

Blood pressure may be lowered after treatment due to dilation of small blood vessels; this is a transient condition that quickly passes, but a short post-treatment rest period is suggested for hypotensive subjects.

Hemorrhagic tendencies

Caution should be used in treating subjects with hemorrhagic tendencies or within 24 hours of surgery on internal organs to avoid a possible increase in bleeding or edema. Also exposure near areas where catheters are inserted is not advised. Pulsed EMF therapy is also contraindicated for subjects with purpura and hemophilia. It should not be applied to subjects who have peptic ulcers, which have bled recently. Although no problem has been encountered in the many effective treatments of dysmenorrhea, the possible increase in menstrual blood flow should be considered.

Hormone levels

As with other pulsed diathermies, some organs may temporarily increase their hormone output after receiving a diathermy treatment. This factor should be considered in evaluating the subject and establishing treatment protocols.

Medication

As with other pulsed diathermies, exposures may tend to enhance the effectiveness of drugs. So this is a factor to consider in subjects where heavy medication may be contraindicated. For example, if Magnopro treatments were conducted during chemotherapy treatment, the delivery of the chemotherapeutic agent could increase in the treated area negatively impacting the subject's tissues in that region.

Pregnancy and epiphyseal centers

Pulsed EMF with the Magnopro is contraindicated over the womb of a pregnant subject and over epiphyseal centers in children.

V. STUDY DESIGN

This was a 6-week study of subjects suffering from acute or chronic knee pain. The effectiveness of the Magnopro in reducing knee pain was evaluated.

Initially, the participant history was taken and a general examination by the PI was performed. History, location, and intensity of the knee pain were assessed and an evaluation of prior therapies occurred.

Each subject self-administered a maximum of 126 treatments, 3 treatments per day over 6 weeks.

Vital signs (blood pressure, pulse/heart rate, and body temperature) were recorded once the subject was admitted into the study. Pain intensity during the first meeting was also assessed.

Subjects diagnosed with chronic or acute knee myalgias and arthralgias could have presented with concomitant symptoms and pathologies that may or may not be related to the source of pain.

Ancillary measures of urine pH and urine specific gravity was obtained from subjects during the first meeting and at the completion of the study in order to capture a more complete and holistic perspective of the subject's progression through the treatment protocol.

VI. EXPERIMENTAL PROCEDURES

A. Number of Subjects Studied

There were a total of 20 subjects allocated to the investigational site approved to conduct this clinical study. All subjects that met the inclusion criteria signed the Informed Consent Form prior to being enrolled in the study.

B. Subject Inclusion and Exclusion Criteria

Subjects experienced chronic pain of six weeks or more at a level of 4 or greater on a 0 - 10 pain rating scale. The study explicitly excluded subjects experiencing pain due to any and all forms of cancer.

Those subjects who met the inclusion criteria and gave their Informed Consent had a General Medical History taken. The subjects then completed:

1. Standards of Pain Assessment and Treatment Scale
2. A Baseline Pain Intensity 100 mm Visual Analog Scale (VAS), and
3. An 11 - Point Pain Intensity Rating Scale

Inclusion Criteria

1. Adult (male or female)
2. Age: 18 years or older
3. Subject has experienced chronic pain of six weeks
4. Pain must be judged to be at least a value of 4 or greater on a pain intensity rating scale, upon entry.
5. Subject must have a clinical diagnosis of relevant healthcare conditions from a healthcare practitioner licensed or legally allowed to practice healthcare
6. Subjects must have normal cognitive and communicative ability as judged by performance in:
 - completing a pain questionnaire (history)
 - completing an 11 point (0- 10) pain intensity rating scale VAS

Exclusion Criteria

1. Inability to directly or indirectly obtain informed consent from subject
2. Pregnant or nursing female, prisoner, mentally retarded subject
3. Subject afflicted with any disease limiting pain evaluation
4. Medical contraindications including subjects with pre-existing heart disease, or subjects with implanted electrical stimulating devices such as cardiac

pacemakers, spinal cord stimulators, bladder stimulators, cerebellar stimulators, metal implants, and phrenic nerve stimulators.

5. Inability to communicate normally, or lacking the cognitive skills necessary to complete the pain intensity and pain relief rating scale
6. Participation in any other pain clinical trial or study
7. Undiagnosed relevant medical symptoms
8. Required use of sedatives and hypnotics or other sensory altering medications
9. Required use of medical devices designed to relieve pain
10. Subjects with hemorrhagic tendencies or within 24 hours of surgery on internal organs will be excluded to avoid a possible increase in bleeding or edema. Also exposure near areas where catheters are inserted is not advised.
11. Subjects with purpura and hemophilia
12. Subjects who have peptic ulcers which have bled recently
13. Subjects where over-medication may be contraindicated. For example, if Magnopro treatments were conducted during chemotherapy treatment, the toxicity of the chemotherapeutic agent could increase in the treated area negatively impacting the subject's tissues in that region
14. Vascular diseases
15. Tumor (metastatic or primary)
16. Infections of the knee joint
17. Inflammatory diseases (e.g., rheumatoid arthritis)
18. Fractures
19. Subject experiencing pain due to a medically diagnosed cancer
20. Subjects currently or expecting to be involved in a medical litigation or malpractice lawsuit.

C. Pain Scale

The most respected healthcare accreditation agency JCAHO (Joint Commission on Accreditation of Healthcare Organizations) implemented a new system “Standards of Pain Assessment and Treatment” on Jan. 1, 2001. It is as follows:

| Pain Intensity Rating Scale | |
|------------------------------------|--|
| Numeric Rating | Explanation |
| 0 | No Pain |
| 1-3 | Low Level Pain – noticeable only when paid attention to |
| 4-6 | Pain Exists – can still perform daily tasks |
| 7-9 | Very Severe Pain – makes concentration difficult but still allows function of daily tasks |
| 10 | Intense, Incapacitating Pain - cannot perform daily tasks |

D. Outcome Variables

The primary efficacy outcome variable was the difference in amount of pain intensity before commencing of the treatment program and the pain intensity after the last treatment session as measured by the Pain Intensity Rating Scale and the VAS scores. Success criterion for this study is defined as a 3 point reduction in VAS or greater reduction in pain from baseline to the VAS level right after the last treatment session on week 6 of the treatment period for each subject. Subjects were allowed to miss one treatment session per day without a need to “make up” the missed session.

Subjects that missed more than one treatment session in any given day were classified as incomplete and the data was not be used in the analysis. Furthermore, subjects that did not complete the 6 weeks of the treatment plan were classified as drop-outs.

Equivalency is defined with respect to a clinically meaningful difference Δ , which for this trial is taken to be a difference of 3.0 or higher between the VAS baseline and VAS final (endpoint) scores for each subject. The formal statistical definition of equivalence is then that the pain reduction at baseline is statistically significantly greater than 3 point less than the pain reduction at the last treatment session.

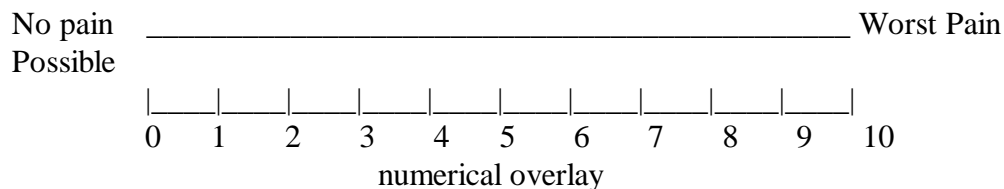
In terms of statistical hypotheses for this self-paired design, let μ_i and μ_f denote the mean pain levels at baseline (initial) and final, respectively. The hypotheses to be tested are

$$H_0: \mu_i - \mu_f \leq \Delta$$

$$H_A: \mu_i - \mu_f > \Delta$$

The hypothesis test was performed as one-sided test, using a significance testing level $\alpha = 0.05$. The primary effectiveness criterion was met if the null hypothesis H_0 is rejected. All statistical analyses were performed using t-test with the SPSS for Windows v8.0 (SPSS Inc., Chicago, Illinois).

The visual analog scale (VAS), reproduced in Appendix F, was used to record the subject’s present pain level without influencing their response by using descriptive terms of pain severity (Campbell et al, 1988; Choiniere et al, 1996; DeLoach et al, 1998; Dixon, Bird, 1981; Jadlos et al, 1996; Myles et al, 1999; St. Marie, 2002; Turk et al, 2001). The scale is a horizontal line. At the left end of the scale are the words “No Pain.” At the right end of the scale are the words “Worst Pain Possible.” The patient is instructed to place a vertical line between the left and right ends of the line to indicate their level of pain. A linear scale of ten equal divisions is placed over the horizontal line by the research nurse to quantify the patient response. Serial responses are compared using the results from the numerical overlay.



As discussed above, the primary efficacy analysis consisted of comparison of the difference between the population means of the reduction of pain from baseline to the last treatment session.

The primary safety analysis is the incidence of device related adverse events. Incidence rates were estimated and presented with confidence intervals. This analysis involved comparing the proportion of patients who do and do not experience each event. No incidents of adverse reactions occurred.

Safety was also assessed by clinical observations related to vital signs and general subject health and a lack of adverse effect reports.

E. Study Termination

The following would result in a subject being terminated from the study:

- Investigator's decision on clinical basis
- Subject request
- Violation of the protocol by the subject or Principal Investigator
- Satisfactory completion of the protocol
- Subject Drop-Outs (defined below).
- Treatment failure (defined below).

F. Drop-outs

- Subjects who missed more than one treatment session in any given day of the treatment plan
- Subjects who did not complete the 6 weeks of treatments.

G. Treatment Failure

Failure of the treatment therapy (Magnopro) to measurably reduce pain by 3 points or more as measured in the baseline and final VAS scores.

H. Concomitant Therapies

The use of all sedatives and hypnotics were prohibited during this study. OTC analgesics were permitted, but only with the permission of the principal investigator or if prescribed by the subject's medical doctor. All concomitant medications and dose levels used during the study were recorded. The use of medical devices designed to relieve pain was also prohibited during this study.

Participants continued with all prescribed medications, which were subject to modifications only by the prescribing physician.

I. Materials and Methods

1. Subject Confidentiality

Upon entry into the study, each subject was assigned a study identification number. These identification numbers, along with the clinic's subject number, and the subject's initials, were used exclusively on the Case Report Forms to preserve subject confidentiality. The investigator kept a master file that related the identification numbers to the subjects should any subsequent subject follow-up be

required. The investigator will keep such information available in their files for a period of five years.

2. Informed Consent

An Informed Consent Form were obtained by the investigator, or designee, in accordance with FDA's regulatory requirements and institutional policy and procedures set down by the Investigational Review Board. (Refer to Appendix A).

3. Case Report Forms

Appropriate Case Report Forms for entry of all measurements were provided. (Refer to Appendix A).

4. Investigation Review Board

Written evidence that the Clinical Investigational Protocol has been reviewed and approved by the Investigational or Institutional Review Board was obtained before initiation of the study.

5. Materials

Each subject was provided one Magnopro device to take home for the treatments.

The subjects were provided the instruction sheet that described the procedure to follow for each treatment (See Section IIIB).

Subjects were provided with VAS forms to fill out and initial right after each treatment session.

6. Methods

a). Study Entry

The investigator was responsible for the final determination of acceptance of a subject into the study and the assignment of an identification number.

b). Documentation on Case Report Form

The Principal Investigator was responsible for completion of all case report forms.

c). Discharge from Study

Subjects were discharged from the study when any of the criteria in Section VI Part E were reached. The reason for the discharge was entered on the appropriate form and signed by the investigator. No cases of discharge occurred.

d). Adverse Reactions

An adverse reaction is considered to be either an occurrence, or "degree of 5" severity reaction, that is beyond the usual clinical experience of subjects undergoing such therapy.

No adverse reactions have been observed during the study.

J. Investigator Responsibilities

1. Read the protocol and submit the appropriate investigator and site information forms to the Investigational Review Board and obtain its written approval to proceed.
2. Obtain signed Informed Consent Forms

3. Select subjects in accordance with the inclusion and exclusion criteria.
4. Assure that the procedures outlined in the Protocol are followed.
5. Treat each subject as outlined in the Protocol until the subject is discharged from the study and the study termination form has been completed.
6. Assure that all Case Report Forms are accurately and thoroughly completed.
7. Cooperate with the periodic monitoring visit by the Project Director.
8. Maintain a master subject log listing all subjects by their names and the clinic assigned subject identification.

K. Responsibilities of the Study Coordinator

The Principal Investigator selected a member of her staff to be the Study Coordinator. The Study Coordinator was responsible for providing the identification number to the subject. The Study Coordinator assisted the Investigator in performance of the protocol study and completion and accuracy of all the necessary documentation.

L. Case Report Forms

As subjects were discharged from the Study, completed Case Report Forms containing all the clinical and pain data were submitted to the Project Director who reviewed the forms for accuracy and completeness.

M. Statistical Analysis

Analysis of the pain intensity data was performed by self-paired t-test.

N. Monitoring Plan

The Project Director periodically visited the investigational site to ensure the Clinical Study was conducted in compliance with the approved Clinical Investigational Protocol and the Principal Investigator adhered to the Clinical Protocol.

O. Definitions

Gauss is an electromagnetic unit of magnetic flux density. It is measured in centimeter-gram-seconds. The levels of magnetic flux density generated by the Magnopro (less than 2 gauss) are considered safe for humans.

A subject's pain intensity, and pain relief, will be measured by using a baseline pain intensity 100 mm visual analog scale, 11-point intensity rating scale, and a 5-word pain intensity category scale. Upon entry, the level of pain must be judged to be at least a value of 4 on a pain intensity rating scale.

An **adverse reaction** is any negative health report, whether related or not, in the opinion of the primary investigator, and will be reported and tabulated.

VII. DESCRIPTION OF THE OBSERVATIONS AND MEASUREMENTS REQUIRED TO FULFILL THE OBJECTIVES OF THE STUDY

A. treatment Protocol

The subjects were required to use the Magnopro device 3 times per day as described in the treatment protocol below.

The intensity level of the Magnopro device was set to six (6) for all treatments.

Morning session (between awakening and 11 AM):

10 minutes program 1 followed by 20 minutes program 4.

Afternoon session (between 1 PM and 5 PM):

10 minutes program 1 followed by 20 minutes program 4.

Evening session (between 7 PM and 12 midnight):

15 minutes program 2.

B. Rescue Therapy

If no pain relief was achieved by this time and the pain is still severe, the Investigator could have elected to provide or recommend appropriate "rescue" therapy. Rescue therapy refers to all other approved methods of pain relief. No cases of rescue therapy were necessary during the study.

VIII. DESCRIPTION OF CLINICAL PROCEDURES, OR OTHER MEASURES TO BE TAKEN TO MONITOR THE EFFECTS OF THE DEVICE IN HUMAN SUBJECTS AND TO MINIMIZE RISK

The subjects completed Pain Intensity Rating right after the administration of each treatment therapy. Therefore, VAS pain intensity was recorded 3 times per day (each time a subject received a treatment) in most cases.

Women of child bearing age could have requested to be tested for pregnancy. Pregnant women were excluded from this study.

The PI or assistant contacted the subjects via telephone on a bi-weekly basis to monitor compliance with the treatment protocol and to identify potential adverse reaction events.

IX. RESULTS

The study objectives were to evaluate the safety, tolerance and efficacy of the Magnopro device on pain intensity in male and female adult subjects age 18 years or older with acute and/or chronic knee pain. The subject population studied included those subjects with joint and soft tissue pain due to injuries and surgeries, chronic sprains and strains, bursitis, nerve injuries, non-specific neuritis or neuralgia and other types of pain, including pain resulting from arthritis.

20 subjects completed the study. Unfortunately, many subjects had to drop out due to the intense treatment schedule that interfered with their travel and family schedules. The high dropout rate significantly slowed down the project completion.

The statistical results are excellent regarding the effect of the Magnopro on knee pain as measured with the Visual Analog Scale (VAS). The statistical significance achieved in lowering chronic knee pain is $p < 0.001$ (see Table 1). Typically, a p value of 0.05 or less is accepted as statistically significant. On the other hand, the clinical effects of the treatment protocol that was used in the study on the physiological parameters that were measured were not statistically significant.

| Parameter | Pre-Treatment Parameter Average | Post-Treatment Parameter Average | Statistical Significance |
|--------------------------------------|---------------------------------|----------------------------------|--------------------------|
| Visual Analog Scale (VAS) | 4.21 | 2.01 | <0.001 |
| Blood pressure - right arm systolic | 132.4 | 130.1 | >0.1 |
| Blood pressure - right arm diastolic | 81.1 | 77.8 | >0.1 |
| Blood pressure - left arm systolic | 131.8 | 128.6 | >0.1 |
| Blood pressure - left arm diastolic | 83.10 | 78.75 | >0.1 |
| Blood pressure - stand systolic | 125.6 | 129.0 | >0.1 |
| Blood pressure - stand diastolic | 78.05 | 81.05 | >0.1 |
| Pulse rate | 69.60 | 71.65 | >0.1 |
| Urine pH | 5.90 | 6.04 | >0.1 |
| Urine specific gravity | 1.0144 | 1.0143 | >0.1 |

Table 1. Statistical Analyses for VAS and Physiological Parameters Measured

REFERENCES

1. Adams R, Victor M, Ropper A (1997). *Principles of Neurology*, seventh edition. McGraw Hill Companies.
2. Bassett CAL, Mitchell SUN, Gaston SR (1989). Pulsing electromagnetic field treatment in ununited fractures and failed arthroeses. *JAMA* (247):623-628.
3. Battisti E, Fortunato M, Giananmeshi F, Rigato M (1998). Efficacy of the magnetotherapy in idiopathic carpal tunnel syndrome. In: Suminic D, ed. Proc IV EBEA Congress, Zagreb, 34-35.
4. Bistolfi F. *Magnetic Fields in Medicine*. Edizione Medical Minerva, 2001.
5. Borgens R, Roederer E, Cohen M (1981). Enhanced spinal cord regeneration in Lamprey by applied electric fields. *Science* (7):213.
6. Bowsher, D. (1987) *Mechanisms of pain in man*. Cheshire, ICI Pharmaceuticals.
7. Cailliet R (1991). *Shoulder Pain*. 3rd edition. Philadelphia: F. A. Davis Company.
8. Campbell, WI, Patterson, CC. (1998). Quantifying meaningful changes in pain. *Anaesthesia* 53(2): 121-5.
9. Choiniere M., Amsel R (1996). A visual analogue thermometer for measuring pain intensity. *Journal of Pain and Symptom Management* 11(5): 299-311.
10. Cumberbatch, EP (1937). *Diathermy*. Baltimore: William Wood & Co.
11. Cumberbatch, EP, Robinson CA (1925). *Treatment of Gonococcal Infection by Diathermy*. St. Louis: C.V. Mosby.
12. DeLoach U, Higgins MS, Caplan AB, Stiff JF (1998). The visual analog scale in the immediate postoperative period: Intrasubject variability and correlation with a numeric scale. *Anesthesia and Analgesia* 86(1): 102-6.
13. Dixon J, Bird H (1981). Reproducibility along a 10 cm vertical visual analogue scale. *Annals of the Rheumatic Diseases*, 1981, Vol 40, 87-89.
14. Einstein A (1977). *Out of My Later Years*. Citadel Press Publishers, NY.
15. Ersek R (1981). *Pain Control with T.E.N.S., Principles and Practice*. St. Louis: Warren H. Green, Inc.
16. Fischer & Co., H.G., (1927) *Diathermy Therapy*. Chicago: H.G. Fischer Co.
17. Goodman R, Bassett AL, Henderson AS (1983). Pulsing electromagnetic fields induce cellular transcription. *Science* (22):1283.
18. Jadlo MA, Kelman GB, Marra K, Lanoue A (1996). A pain management documentation tool. *Oncology Nursing Forum* 23(9): 1451-2.
19. Jorgensen WA, Frome BM, Wallach C (1994). Electrochemical therapy of pelvic pain: effects of pulsed electrochemical fields (PEMF) on tissue trauma. *Eur J Surg; Suppl* 574:83-86.

20. Kristensen JD, Svensson B, Gordh T (1992). The NMDA-receptor antagonist CPP abolishes neurogenic 'wind-up pain' after intrathecal administration in humans. *Pain*; 51(2):249-53.
21. Leclaire R, Bourgoin J (1991). Electromagnetic treatment of shoulder periarthritis: a randomized controlled trial of the efficiency and tolerance of magnetotherapy. *Arch Phys Med Rehab*, (72)284-287.
22. Lente RW (1859). Cases on un-united fracture treated by electricity. *NY J Med* (5):317.
23. Liboff AR, Strong DM, Williams T, Wistar R (1984). Time varying magnetic fields. Effect o DNA synthesis. *Science* 223:818.
24. Lorrain P, Corson DR, Lorrain F (2000). *Fundamentals of Electromagnetic Phenomena*. W.H. Freeman, New York.
25. McLean MJ, Engstrom S, Holcomb RR (2003). *Magnetotherapy: Potential Therapeutic Benefits and Adverse Effects*. TFG Press. New York.
26. Myles PS, Troedel S, Boquest M, Reeves M (1999). The pain visual analog scale: Is it linear or nonlinear? *Anesthesia and Analgesia* 86(6): 1517-20.
27. Nelson P (2003). *Biological Physics*. WH Freeman, New York.
28. Prasad P (2003). *Introduction to Biophotonics*. John Wiley, New York.
29. Rosch PJ, Markov M. (2004) *Bioelectromagnetic Medicine*. New York: Marcel Dekker.
30. Simunovic Z. (2000) *Lasers in Medicine and Dentistry: Basic science and up-to-date clinical applications of low energy – level laser therapy*. Vitagraf Publisher, Croatia.
31. Siskin BF, Walker J (1995). Therapeutic aspects of electromagnetic fields for soft-tissue healing. *Advances in Chemistry Series 250*. Washington DC: American Chemical Society, 227-285.
32. St. Marie B, American Society of Pain Management Nurses (2002). *Core curriculum for pain management nursing*. Philadelphia: Saunders.
33. Szent-Gyorgyi A (1976). *Electronic Biology*. Marcel Dekker, New York.
34. Travell JT, Simon DG. (1983) *Myofascial Pain and Dysfunction –The Trigger Point Manual*. Vols 1 and 2. Williams & Wilkins.
35. Turk D, Melzack R. (2001). *Handbook of pain assessment*. New York: Guilford Press.
36. Wall PD, Melzack R (eds.) (1989). *Textbook of Pain*, 2nd ed. (pp. 1-18). Edinburgh: Churchill Livingstone.
37. Warnke U. (1983) The possible role of pulsating magnetic fields in the reduction of pain. Elsevier Biomedical Press, *Pain Therapy*, R. Rizzi and M. Viseentin eds.
38. Warnke U, Ambromn G, Muxeneder R. (1997). *Laser and Magnetic Field Therapy in Veterinary Medicine - Bases and Application*. Enke, Stuttgart.