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THE EFFICACY OF ELECTROMAGNETIC BONE GROWTH STIMULATORS ON DELAYED AND NON-UNION FRACTURES ON META-ANALYSIS

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THE EFFICACY OF ELECTROMAGNETIC BONE GROWTH STIMULATORS ON DELAYED AND NON-UNION FRACTURES: A META-ANALYSIS

By

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ABSTRACT

THE EFFICACY OF ELECTROMAGNETIC BONE GROWTH STIMULATORS ON DELAYED AND NON-UNION FRACTURES: A META-ANALYSIS

By

Tara Angela Yeske

Purpose: The purpose was to determine the efficacy of electromagnetic bone growth stimulators on healing delayed and non-union fractures.

Methods: All eligible studies from MEDLINE and CENTRAL were compiled and reviewed by two reviewers. Inclusion criteria included any randomized controlled or controlled clinical trial comparing a bone growth stimulator to a sham control. All disagreements between the two primary reviewers were adjudicated by a third reviewer. Abstracted data was used to estimate a relative risk.

Results: Only four articles met all inclusion criteria and data was extracted for the meta-analysis. The primary finding of the meta-analysis was a summary random effect risk ratio of 2.62, with a 95% confidence interval of 0.78 to 8.78. The test of homogeneity was highly significant ($Chi^2 = 21.91$, 3 d..f., $p < 0.0001$). Out of the four studies, only Barkers's favored the control over treatment (RR = 0.91).

Conclusion: The primary findings from the random effects method conclude that there was no statistically significant evidence that bone growth stimulators promote healing on delayed or non-union fractures. However the secondary analyses using a fixed effect analysis showed a similar but statistically significant effect of bone growth stimulators on healing compared to sham control. Both analyses have significant heterogeneity and a small amount of included studies.

A successful man is one who can lay a firm foundation with the bricks others have thrown at him.

-David Brinkely

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CHAPTER 1

INTRODUCTION

Overview of the Problem

Delayed union is, "the cessation of the periosteal response before the fracture successfully has been bridged." (Marsh, 1998). Fractures that are delayed unions have a retardation of the normal process of bony consolidation. Delayed union does not imply that the fracture will never heal, just that the process is slowed. Nonunion fractures are defined as being, "A bone that fails to unite or heal completely. Diagnosis of nonunion is established when a minimum of nine months have elapsed since the injury and the fracture site shows no progressive signs of healing for a minimum of three months without a complication from synovial psedoarthrosis." (Venes & Thomas, 1997). Fractures of this type are not expected to heal without further intervention such as surgery.

Diagnosis of nonunion or delayed union fractures is made on clinical symptoms including pain, range of motion, and radiological evidence of callus formation (Panagiotis, 2006). There are many reasons why fractures fail to heal. These risk factors include inadequate immobilization, comminuted and devascularized bone, poor vascularity of fracture fragments and surrounding soft tissue, infection, prior irradiation, presence of bony defects, systemic factors such as malnutrition or chronic illness, medical related conditions, and smoking (Saleh & Hak, 2001). Nonunion and delayed union can be treated either surgically or non-surgically. Bone grafts, internal fixation, plate fixation, and intramedullary nailing are examples of invasive surgical techniques commonly used for fractures

(Panagiotis, 2006). Osteoinductive molecules and external electromagnetic bone stimulators are two new, less invasive options for nonunion therapy. Shortly after the first report of using oscillating electromagnetic fields to treat nonunions in 1983, the Food and Drug Administration approved the use of pulsed electromagnetic fields for clinical use for treating nonunion fractures in humans (Otter et al., 1998). Health insurance companies have already added these devices and approved them for billing of treatment. In a statement put out by Aetna (2006), they cite direct current electrical bone growth stimulators medically necessary for conditions including non-unions, failed fusions, congenital pseudarthrosis, delayed union, and for patients at high risk for spinal fusion. Insurance companies are pushing for the use of bone growth stimulators in order to avoid open reductions or bone grafts that would, in consequence, accrue further costs.

Clinicians, as a profession, must continually educate themselves on current science by reading various scientific journals. They are bombarded by a plethora of academic articles and must filter through them and judge which ones are truly scientifically sound. Electromagnetic bone growth stimulators are a relatively recent modality and there are conflicting results from various scientific studies disputing their efficacy in regards to bone regeneration. This study will provide answers about bone growth stimulators using only the strongest scientifically based studies, and allow the clinician to make an educated decision of whether to use to modality in practice. Not only will new statistics be generated, but readers can also use the meta-analysis as a tool to quickly review

all the scientifically sound articles on the topic. In order to understand the actual efficacy of bone growth stimulators on nonunion and delayed union fractures, a systematic review must be conducted on the current literature.

Significance of the Problem

Five to ten percent of fractures become delayed unions and approximately one percent becomes nonunion fractures (Einhorn, 1995). With lower extremity fractures, the risk of delayed or non-union increase dramatically, with 29% becoming delayed unions and 19% becoming nonunion fractures (Coosemans et al., 1988). Delayed and non union rates for open tibial shaft fractures range from 16-60% in lower grade fractures to 43-100% in more severe open injuries (Caudle & Stern, 1987; Sanders et al., 1994; Reimer et al., 1995). If a delayed union or nonunion fracture is left untreated it can result in arthritis in the joint, loss of range of motion, prolonged hospital stays, multiple operations like plates, internal fixation, and bone grafts, long periods of immobilization, increase expenses, and decrease in the quality of life. Fractures that heal in the malunited position may require osteotomy to correct alignment or rotation (Younger & Chapman, 1989). "Particularly severe injuries may become recalcitrant nonunions, requiring multiple operative interventions over months to years to achieve union." (Saleh & Hak, 2001).

Only one meta analysis looking at the effectiveness of electromagnetic bone growth stimulators on delayed union and non union fractures was registered on the Cochrane Library, and merely few have been published in journals. This study titled *Electromagnetic Field Stimulation for the Treatment of Delayed*

Union of Non-union of Long bones by Punt et al. (2004) is an unfinished, ongoing study which only reviews long bones and neglects to address the many predisposed anatomical sites with poor blood supply. There is currently a controversy over whether bone growth stimulators are effective and specifically for what conditions. *Effect of Electric Stimulation of Musculoskeletal Systems: A Meta-Analysis of Controlled Clinical Trials* by Akai and Hayashi (2002) proves there are positive effects when used for tissue healing. Table 1 compares these meta-analyses along with the studies *Electromagnetic Fields for the Treatment of Osteoarthritis* by Hulme and associates and *Electric Stimulation and Hyperbaric oxygen therapy in the treatment of Nonunions* by Karamitros, Kalentzos, and Soucacos (2002, 2006). To date there is not one large definitive trial on the efficacy of bone growth stimulators for delayed and non-union fractures. Because there are so many scientific studies being published on this topic, it is difficult to sift through the contents and discern which studies are truly scientifically sound in order to compound a true result. The studies that have been published are outdated with the most recent collection of studies being from 2001. This gap in literature fails to identify current studies and will be filled by this meta-analysis.

Problem Statement and Research Plan

The purpose of this systematic review is to evaluate the efficacy of electromagnetic bone growth stimulators on delayed union and nonunion fractures at all sites based on randomized controlled trials conducted on humans. For this review delayed union fractures will be classified as no healing at the site with in three or more months and non-unions defined as failure to unite beyond six

months. All articles will go through a three step screening process. Article titles found in the search will be initially screened. If the title and abstract appears relevant to the review, the article will then be read in order to identify if it meets eligibility criteria. Only randomized and controlled clinical trials will be considered. Randomized controlled trials are clinical trials that have a control treatment allocated by a random process. A controlled clinical trial is any study that allocates by a pseudo-random process like coin flips or social security numbers. If the study meets these criteria, data extraction will take place and it will then be included in the review. The quality of studies will then be assessed according to the Jadad score and Cochrane approach to quality assessment for inclusion. See Appendix A for the assessment characteristics.

Need for the Study

There have been numerous studies done on stimulating bone growth with electromagnetics and ultrasound techniques although only a few were performed using the randomized clinical trial design. Of the four previous published reviews, only one by Punt and associates (2004) concentrated on bone growth stimulators and their efficacy with delayed and non-union fractures. This same review is being researched on long bones including the tibia, fibula, femur, and radius. Other sites that traditionally have poor blood supply like the scaphoid, are not included. This study involves pulsed and non-pulsed electromagnetic bone growth stimulators and is currently being conducted. A meta-analysis by Akai and Hayashi (2002) used pulsed electromagnetic fields to test efficacy on bone healing and soft tissue healing. Because of the criteria, only studies published

from 1966-1999 were included. This leaves a time gap where the intervention has evolved. More current studies need to be compounded in order to analyze the true efficacy of bone growth stimulators. The methodology of this review researches two different efficacies, which skew the results of the true effectiveness on non-union and delayed union fractures (Punt et al., 2004; Akai & Hayashi, 2002). Out of the forty-nine studies reviewed, only twenty-eight were used in the meta-analysis, a limited amount of studies. This study did not disclose their statistics analyzed by ROMA 88. Their reported general findings showed no proof that bone growth stimulators had a specific effect on health, but had positive findings when used on tissue repair.

Another meta-analysis conducted by Hulme and associates (2002) focused on pulsed electromagnetic fields and their efficacy healing osteoarthritis. All randomized clinical trails and controlled clinical trials published before 2001 were used. Even though controlled clinical trials were included, only three out of 102 studies met the inclusion criteria (Hulme et al., 2002). Due to the low number of literature, no clinically important results were produced. A review titled *Electric Stimulation and Hyperbaric Oxygen Therapy in the Treatment of Nonunions* evaluated studies that used electric stimulation in combination with hyperbaric oxygen (Karamitros et al., 2006). The results of pulsed electromagnetic fields alone cannot be determined from this study because of its use in combination with hyperbaric chambers. Being the most recent systematic review conducted, no new information was generated because a meta-analysis was never ran. The problem why previous studies have not efficiently addressed the topic includes a wide

distribution of various types of injuries, various types of outcome assessments, small number of included studies, and a time gap of current literature exists. Also many of the reviews do not consider selection bias by only searching for journals off electronic databases and with articles that are only published in English. This study will concentrate on the efficacy electromagnetic stimulation has on delayed union and nonunion fractures at all sites. All randomized and controlled clinical trials published until the present date will be included in the review. Only studies testing bone growth stimulators will be used. This includes direct current, PEMFs, and capacitive coupling. The results of the review will provide a scientifically sound consensus on bone growth stimulators and will aid the decision of whether to utilize the modality in general practice for clinicians in the healthcare field. Once the systematic review is completed, an attempt at a meta-analysis to get a summary result will be made.

Research Questions

With all the conflicting data on efficacy of bone growth stimulators regenerating bone, this meta-analysis will compare only the studies of the highest scientific nature by using randomized and controlled clinical trials in order to quantify the true benefit of the modality. The statistical analysis will be concentrated on the following questions:

1. What is the efficacy of electromagnetic bone growth stimulators on delayed union and non-union fractures at all sites?

2. Are there differences in results of studies performed as randomized controlled trails compared to clinical controlled trials?

3. Does the blinding of outcome assessors affect the results?

4. Does the methodological quality of studies affect the outcome when looking at both sensitivity analyses?

Definition of Terms.

Delayed union: an ununited fracture that continues to show progress towards healing or that has not been present long enough to satisfy an arbitrary time standard for nonunion (Phieffer & Gould, 2006). It is usually diagnosed when there is failure to see normal healing of the bone on radiographic evidence within three to six months of the injury depending on the fracture site (Punt et al., 2004).

Electric Stimulation: there are three distinct forms, direct electric current, pulsing electromagnetic fields (PEMFs), or capacitive coupled electric energy. The direct electric current uses a generator to deliver electric energy by surgically implanted electrodes into the fusion bed. PEMFs are a time varying current that travels through metallic coils at a certain duration and intensity. Capacitive coupling charges two metal plates that are attached to a voltage source and produces electrical field. Both PEMFs and capacitive coupling utilize electrodes (Oishi & Onesti, 2000).

Meta Analysis: a statistical technique for combining the results of a number of individual studies to produce a summary result. It is not synonymous with a systematic review (Khan et al., 2003).

Nonunion: when the normal biological healing process of the bone ceases so that complete healing will not be achieved without further treatment (Pheiffer & Gould, 2006). The United States Food and Drug Administration quantifies a

nonunion as a fracture that has occurred at least nine months previously and has not shown any radiograph signs of progression towards healing for three consecutive months (LaVelle, 1998).

Pseudoarthritis: the formation of a false joint where the fibro cartilaginous cavity is lined with synovium and produces synovial fluid (Panagiotis, 2006).

Radiological Criteria: following x-rays, radiological signs as evidence of union of a fracture such as loss of distinction at the fracture gap, cortical bridging, and trabecular bridging (Simonis et al., 2002).

Systematic Review: a method for reviewing and evaluating scientific literature. The review evaluates and interprets all available research relevant to a particular question. It identifies all relevant primary research and standardizes study quality so that only studies of acceptable quality are synthesized (Glasziou et al., 2001).

CHAPTER 2

LITERATURE REVIEW

Non union and delayed union fractures are a common occurrence among bones with poor blood supply. Traditionally in the past only surgical options were considered for repair. Just recently have modalities like bone growth stimulators and ultrasound been used in an attempt to enhance bone growth and fracture repair. In order to understand the scientific basis behind the modality, the history of bone growth stimulators will be discussed. Also literature will be reviewed regarding the process of using meta-analysis as a research tool.

Anatomy and Physiology of Bone

Bones are organs that contain several different tissues including osseous tissue, nervous tissue, cartilage, muscle, and epithelial tissue. There are two parts to the bone, the compact bone which is the dense outer layer and the cancellous or spongy bone which lies internal to the compact bone (Marieb, 2001). The entire surface on the outside of the bone is protected by a double layer membrane called the periosteum. Dense, irregular connective tissues make up the first layer of the periosteum. The inner osteogenic layer is made up of osteoblasts, bone forming cells, and osteoclasts, bone reabsorbing cells (Watson, 1979). The periosteum is supplied with nerve, lymph, and blood vessels which enter the bone by the nutrient foramen (Marieb, 2001). The endosteum is a connective tissue that covers internal bone surfaces including the cancellous bone and marrow which also contains osteoblasts and osteoclasts.

Bone remodeling is caused by bone deposit and resorption in the periosteal and endosteal surfaces (Marieb, 2001). The actual process that triggers calcification of the matrix is controversial although researchers do know that in order for bone deposits to be made, there are key products needed. When calcium and phosphate reach a certain level, tiny crystals are formed. Another product required for calcification is matrix proteins in order to bind the calcium. Alkaline phosphate which is shed by osteoblasts is a key ingredient for mineralization (Marieb, 2001).

During bone resorption, osteoclasts from stem calls in the bone are turned into macrophages. These macrophages move around the bone surface and dig pits called resorption bays as they break down the matrix. The outside of the osteoclasts secrete lysosomal enzymes and acid. These two substances aid in digesting the matrix and converting calcium and salt into soluble forms that can be transported through the blood (Marieb, 2001).

There are two systems in the body that control bone remodeling. These are the negative feedback hormonal mechanism and the body's response to mechanical and gravitational forces on the skeleton. The hormonal mechanism is an interaction between the parathyroid hormone (PTH) and calcitonin. PTH is released when blood calcium levels decrease and stimulate osteoclasts to reabsorb bone which in turn releases more calcium into the system. Calcitonin is secreted when blood calcium levels increase and inhibits bone reabsorption. It also encourages calcium deposits in the bone matrix reducing blood calcium levels.

These two elements monitor the body's calcium level to keep it at a consistent homeostasis.

The body's response to mechanical stress and gravitation forces is based off of Woolf's law which states that bones grow or remodel in response to the forces placed on it. In this mechanism the forces are muscle pull and gravity (Marieb, 2001). When bone is loaded it bends and causes compression forces on one side and tension forces on the opposite. Deforming bone causes an electrical current with the compression and tension regions of the bone being oppositely charged. This suggests that electrical signals direct the remodeling process. Bone tissue tends to deposit in negatively charged regions while absorption occurs in areas of positive charges. The theory of this mechanism is that electrical fields prevent PTH from stimulating osteoclasts which decrease bone absorption at the site (Marieb 2001).

The Process of Osteochondral Regeneration

The healing time for simple fractures can be six to eight weeks or longer for large weight bearing bones and complicated fractures. There are four major phases of the healing process. The first phase is hematoma formation. After the fracture blood vessels in the bone, periosteum, and tissue are torn and hemorrhage making a massive clot of blood at the fracture site. The bone cells around the fracture site are deprived of nutrients and die. This causes the tissue to become swollen, painful, and inflamed. Fibrocartilaginous callus formation is the second phase. Within a few days of the fracture a callus from the thrombus is formed out of fibroblasts, collagen, proteoglycans, and chondrocytes (Otter et al., 1998).

Capillaries grow and phagocytes clean the hematoma. Fibroblasts and osteoblasts are sent to the fracture site to rebuild by forming spongy bone and making collagen fibers.

The third phase is named the bony callus formation. During this phase new trabeculae bone in the callus starts to harden. This phase initiates three to four weeks after the injury and ends in a firm union in two to three months (Marieb, 2001). Bone remodeling, the last phase, begins during the third phase and continues for several months after the bony callus is remodeled. Excess material is removed and compact bone is laid down to reconstruct the shaft walls. In the end the bone resembles its original structure before the fracture. With normal healing, over time the callus is invaded by blood vessels and the cartilaginous material is removed while the tissue becomes calcified. However this process does not occur with a true nonunion fracture. It is at this time in the bone regeneration process that many clinicians choose to surgically treat the fracture before it becomes a delayed or nonunion.

Factors Affecting Bone Regeneration

Bones fail to unite not just because they are poorly vascular or were immobilized improperly. There may be underlying factors that inhibit the bone regeneration process itself. Chronological age plays a role in bone regeneration. It is proven that it takes bones longer to heal in the elderly because they have poor circulation (Marieb, 2001). There are many pathological conditions that interfere with bone growth. There have been examples of infected growth plates where the plate is partially or completely destroyed by the infection process (Hall, 1990).

During the growth phase infections can inhibit or stimulate abnormal intramembranous ossification. Children with anemia may have problems with bone growth. Their body has an abnormal increased need of space for hematopoietic tissue. This causes an increase in marrow at the expense of cortical bone and is commonly found in long bones and the skull. The replacement of compact bone leaves it with a porous appearance like dry bone (Hall, 1990). Metabolic processes like hyperthyroidism causes an abnormal pattern in bone growth. In a healthy body, the thyroid hormone stimulates replacement of cartilage in long bones with bone tissue. The amount of thyroid hormone secreted is inadequate for normal bone growth in a person with hyperthyroidism. The pituitary gland secretes growth hormone which is responsible for the division of cartilage cells in epiphyseal disks. Without this hormone, the long bones fail to develop causing dwarfism (Marieb, 2001). Other diseases associated with abnormal bone formation include osteomalacia where bone is inadequately mineralized, osteoporosis where bone resorption out paces bone deposits, and Pagets disease where Paget bone replaces the marrow cavity.

Diabetes and malnutrition have been linked to the process of bone growth. For optimal bone growth the body needs proteins and minerals including calcium phosphate, magnesium, and manganese. Vitamin D aids in the absorption of dietary calcium. Vitamin A balances the deposit and removal of bone by being involved in osteoblast and osteoclast activities. Collagen synthesis requires Vitamin C. Without it osteoblasts produce less collagen in the intercellular

material of the bone tissue resulting in bones that are abnormally slender and fragile.

History of Electromagnetics on Remodeling Bones

Electromagnetism, the physics of the electromagnetic field, is responsible for the interaction of atoms, which make up the main foundation for biology and medical field. The 1950's marked an era when the first piezoelectric properties were reported in Japan by Fukada and Yasuda (Ryaby, 1998). It was also during this time that bone tissue was discovered to have electric properties. Other research was also conducted by Bassett and Friedenberg (1962) on the osteogenesis influence of bioelectrical properties of bone. Friedenberg (1966) was the first researcher to successfully treat a non-union ankle in their clinic with electromagnetic stimulation.

In 1957, Fukada discovered that mechanical loading of the bone generates an electrical potential in the bone tissue (Fukada & Yasuda, 1957). He found that when a bone is stressed, there is an electropositive charge on the convex side and an electronegative charge on the concave side. This finding coincides with Wolff's law that bone remodels at areas of compression and reabsorbs at areas of tension (Liboff, 2006). Studies prove that walking produces mechanical strains lower then 10 Hz while postural muscle activity produces higher frequencies 20 to 30 Hz (Antonsson & Mann, 1985). Electronegative charges can be found at sites with active bone growth including growth plates and epiphysis because osteoblasts are activated by negative charges. Research has shown that bone

growth peaks around the cathode, the negative electrode, and decreases around the anode, the positive electrode (Liboff, 2006).

Bioelectrical Properties in Bone

Potential differences exist in all living tissue. A steady resting potential from microvolts to more then one hundred millivolts has been recorded in biological systems. These differences undergo changes with metabolic processes, injury, illness, mechanical stress, and different states of consciousness (Friedenberg & Brighton, 1966). There are many natural origins of direct currents found in tissues including ionic gradients and ion transfers across membranes, structure of tissue with polarized molecules, the semiconductor mechanism in tissues, and the cell metabolism itself. Strained electric potential signals for regulation of cellular processes such as bone repair and remodeling. Since all tissues are subjected to dynamical mechanical stress, they may use these electrical signals as a regulation component in the mutinous and repair of tissue function (Ryaby, 1998). For example, bone and cartilage are mechanosensistive. Electric properties from the mechanical load cause streaming potentials produced from fluid flowing through the charged extra cellular matrix. These potentials inform the cells to alter skeletal remodeling due to the changing load (Ryaby, 1998). Friedenberg and Brighton (1966), conducted a study to measure the electrical potential in human bones. Skin potential differences were taken with electrodes from the leg and thigh in thirty six humans, sixteen of which had healing tibial fractures. They found a typical curve pattern in the electricity of healthy bones. In non-fractured bones, the epiphysis was positively charged with respect to the

subepiphysis and the metaphysis was negative in respect to the epiphysis. In fractured bones the entire shaft down the epiphysis was electrically negative and a secondary increase in electric negativity was found over the fracture site. With healing of the fracture, the electric curve returns to normal. The fact that electricity at the fracture site is markedly negative supports that either bone growth is stimulates negative charges, or that the electrical negativity at the fracture site was a result of the fracture. This curve pattern is consistently similar on the skin and periosteum to the curve on the bone and indexes the magnitude and disposition of direct currents in bones.

This phenomenon was also observed in mammalian and amphibian bones. Bassett and Becker (1962) conducted a study which put two electrodes, one posterior and one anterior to monitor the electric activity of amphibian bones being bowed. The pressure was applied so the bone would deform concave posterior. When pressure was exerted, immediately the posterior electrode recorded negative electricity that slowly decreased until the force was removed. After the force ceased, the anterior electrode briefly became negative. Deformation in the opposite direction was applied and the same results were observed. The results confirm that these potentials were caused either by piezoelectric properties or a displacement potential. The displacement potential occurs when a number of molecules are bent in the same way displacing free charge carriers from in to outside the molecules.

The amplitude of the electrical potential depends on the rage and magnitude of bony deformation. The polarity is determined by the direction of

bending (Bassett & Becker, 1962). When bone deforms osteoclasts inundate the surface of tension while osteoblasts swarm the area of compression. This happens so bone remodels in a better way to cope with the stress. It is believed that mechanical deformation causes potentials in bone because direct current has been linked with cellular migration, tumor formation, morphogenesis, and regeneration of amphibian limbs (Bassett & Becker, 1962). Since stress potentials from walking or deforming bone influence the activities of bone cells, it is possible that electricity is the underlying factor between mechanical stress and bone remodeling (Watson, 1979).

Many studies that have been performed prove that electromagnetic fields modify the bone growth process. Norton (1974) completed research on rooster chicks that show bone growth orients to the positive electrode when the induced charge on the bone is negative. In his studies Friedenberg (1966) observed that stimulated bone formation surrounds the cathode and radiates out in a manner that coincides with electrical field lines. The release of hydrogen at the cathode occurs instead of consuming oxygen and makes hydroxyl radicals that contribute to the alkalinity of the tissue making it more favorable to calcification (Watson, 1979).

There are various theories behind the origins of electric potential in bone. One theory is based on piezoelectricity. This is defined as the generation of electrical current from the stress of bone crystals and is dependent on the rate and magnitude formation (Friedenberg & Brighton, 1966). This theory supports why the concave side of bones are negative compared to the convex. The streaming

potential is an alternate theory. This states that electrical potentials are a function of the rate of fluid flow in the growth area due to different tissues being comprised of dissimilar components with inherent surface charges. For example, when a bone bends small channels in the cortex deform which causes movement of liquid towards the surface of tension. If the mobile ions are positive, then the surface under tension will turn positive. This theory explains why measurements of bone potential vary with the rate of load on application.

When outside electrical potentials stimulate bone it is hypothesized that one of two things happen physiologically. The electrical field may prevent the parathyroid hormone from stimulating osteoclasts at the fracture site, which decreases bone absorption leading to the formation of more bony tissue. Or the electrical fields induce products of growth factors, which stimulate osteoblasts (Marieb, 2001). There are many factors to consider for successful clinical application of electric stimulation. Friedenberg believes that current density and voltage or field strength is involved while Lavine and Connolly believe that the passage of electrical current across the fracture gap stimulates healing (Watson, 1979). It is believed that a threshold of energy needs to be produced, below which no regeneration occurs. Bassett et al. (1977) stress the importance of pulse parameters and concluded that the field strength at a nonunion is 1.2-1.6 mV/cm.

Scientific Theories Behind Electromagnetic Stimulators

Several theories explain the potential bone healing qualities of electromagnetic stimulators. These include strained general electric potentials being signals used for regulating cell processes including bone regeneration and

remodeling. This suggests that all tissues that get stressed may use electrical signals in the maintenance and repair of tissues (Ryaby, 1998). Bone growth stimulators are a device made to mimic this electrical signal.

There are three different ways to use the stimulators to treat nonunion and delayed union fractures. Direct current stimulation is conducted with an implanted electrode and is the most invasive of the three. Electromagnetic stimulators work by inductive coupling that uses time varying magnetic fields that emit a pulsed electrical current through a coil placed on the fracture site (Punt et al., 2004). Capacitive coupling stimulators use opposing electrodes that are also placed over the fracture site (Liboff, 2006). Both capacitive and inductive coupling are noninvasive.

Electromagnetic stimulators also vary in being pulsed or non-pulsed. These pulsed waveforms have become the standard for the bone growth stimulator industry because the pulses mimic higher frequency potentials that are seen during impact loading during bone tissue (McLeold et al., 1995). Studies have shown that pulsed electromagnetic currents can differentiate bone cells, reduce osteoclast absorption, increase vascularity, and increase the rate of osteoblasts in bone formation (Luben, 1991). A study conducted by Robert Luben (1991) chronicles the hypothetical molecule mechanism that accounts for the effects of low energy electromagnetic fields on bone cell metabolism and it effects on hormone regulation of osteoblast function and differentiation.

Research on Electromagnetic Stimulators

Research has shown successful results for all three stimulators. Brighton et al. (1981) reported an 84% healing rate with nonunions using direct current. This clinical study initiated at the University of Pennsylvania and expanded through the United States, included 175 patients with 178 nonunions. To be included, the patients had serial roentgenograms to diagnose their nonunions. Nonunion was defined as the absence of progressive signs of healing for over five months. An implanted direct current stimulator with four cathodes was used for a period of twelve weeks. The intensity was set at twenty microamperes of direct current. Of the 178 nonunions, 149 achieved solid bone healing (Brighton et al., 1981). Along with being an invasive technique, the other negative aspects to using direct current is the by products of consumption of dissolved oxygen and an increase in pH levels at the electrode-tissue surface (Otter et al., 1998).

Pericles Diniz and colleagues (2002) studied how PEMF stimulation affected osteoblasts in different stages of maturation to see if the number of cells or differentiation was changed. Using cell cultures, cell proliferation, differentiation, and area of mineralized matrix was measured after being stimulated. The researchers found that PEMF affected the osteoblasts in early stages of the culture during cell proliferation and differentiation by increasing bone tissue-like formation. Although the stimulatory effect during the mineralization stage decreased bone tissue-like formation. Overall the stimulatory effect was most associated with enhancing cellular differentiation but not increasing the amount of cells (Diniz et al., 2002).

In a study conducted on delayed unions with incomplete healing after 16 to 32 weeks, Sharrard (1990) showed that PEMFs provided a substantial benefit than a surgical intervention. This double blind trial of PEMFs was performed on patients with tibial osteotomies and resulted in doubling the number of patients at advanced stages of healing within the first 60 days of treatment. Sharrard treated forty-five patients with tibial shaft fractures. All were immobilized in plaster and given electromagnetic stimulation units for twelve weeks. Twenty patients had an active unit while twenty-five patients were fitted with dummy control units. A radiologist's assessment concluded five unions, five progress to unions, and ten with no progress to union in the active group. In the control group there was one union, one progress towards union, and no progress in twenty three. An orthopedic surgeon's assessment showed union in nine fractures and absence in eleven of the active group. The control group presented with three unions, twenty-two without unions. These results were significantly in favor of the active group, $p=0.02$ (Sharrard, 1990).

Even though effective experiments have been reported, there still remain many questions about the science and physiology behind the bone growth stimulators. Currently it is not known the degree that applied magnetic field or induced electrical fields are responsible for the biological response (Punt et al., 2004). Since the stimulators range on an electrical spectrum from 1 Hz to 1 MHz, the most beneficial frequency is still debated. Currently the literature concludes that electric frequencies at or lower then 120 Hz are maximally responsive to bone remodeling activity (McLeod & Rubin, 1990).

Performing a Systematic Review

Research that is relevant to the health care industry is scattered among a plethora of journals. It is the professional's responsibility to determine which journals are scientifically sound and choose the research from those articles to help inform their clinical practice. It is difficult to keep well informed on many topics particularly those issues that are controversial. The systematic review is a technique that attempts to identify all relevant articles on a topic. Relevant studies are categorized according by their study design and quality. Systematic reviews focus on a single question, in this case the efficacy of bone growth stimulators. If enough similar articles can be found that present quantifiable data then a meta-analysis, the process of calculating a summary effect estimate, can be generated.

Performing a Meta-Analysis

A meta-analysis combines the results of several studies of a related research hypothesis. Each study is weighted according to size and sometimes trial quality in order to generate a summary effect estimate. Its purpose extends beyond simply combining the effect from a group of studies. Meta-analyses can also identify important variations between studies i.e., heterogeneity and can explore origins of this variability. Not all systematic reviews will lead to a meta-analysis. If there is insufficient data or studies are too dissimilar then a meta-analysis may not be a logical choice.

Published Meta-Analyses

In order to create the screening process for inclusion of articles, various published meta-analyses on bone growth stimulators were researched. The one protocol most similar to this study was conducted by Punt, den Hoed, and Stijnen (2004). Their study, titled *Electromagnetic Field Stimulation for the Treatment of Delayed Union or Non-union of Long Bones*, used pulsed and non pulsed electromagnetic fields on fractures of long bones. Many elements of this study's protocol are derived from it.

A review titled *Electric Stimulation and Hyperbaric Oxygen Therapy in the Treatment of Nonunions* used electric stimulation in combination with other therapy in order to heal delayed and non-union fractures (Karamitros, Kalentzos, & Soucacos, 2006). Pulsed electromagnetic fields, direct current, and hyperbaric oxygen were some of the interventions used. Since this study was a review, a meta-analysis was not conducted and no statistics were gathered.

Researches Akai and Hayashi used articles from 1966-1999 in order to test the effects of pulsed electromagnetic fields on bones, soft tissue, and joints (2002). Their study was scientifically sound and masked reviewers during data extraction. In their meta-analysis twelve out of twenty studies were reviewed on bones and sixteen out of twenty-nine studies were reviewed on soft tissue and joints. Their results show positive findings when PEMF is used on tissue repair although have no specific effect on health or bone healing.

Electromagnetic Fields for the Treatment of Osteoarthritis focused on the use of PEMF to treat osteoarthritis (Hulme et al., 2002). Because osteoarthritis is defined as degeneration of cartilage within a joint, this wearing down of bone

cells can be related to a bone fracture. Out of 102 studies only three met the inclusion criteria for this meta-analysis. No clinically important results were generated due to the low number of literature.

Jadad Quality Assessment Tool

Numerous scales and checklists have been developed to evaluate the quality of randomized clinical trials. The Jadad Scale, originally used to assess the quality of articles on pain relief, has been extensively used to assess study quality in other clinical areas. In a study published by Moja (2005) examining 965 systematic reviews, the most commonly used tool for quality assessment was the Jadad scale. It is a scale that is recommended by the Cochrane Musculoskeletal Group in the preparation of their Cochrane systematic reviews (Towheed, 2006). The Jadad Quality Assessment is a seven question scale that measures study design and reporting quality with a numerical score from 0-5, with zero being the weakest and five being the strongest (Jadad, 1996). The first five items are indications of good quality with each counting as one point towards the overall score. These five items are 1) a randomized study, 2) reporting the method of randomization, 3) being double-blind, 4) describing the method of double-blinding, and 5) a description of withdrawals and dropouts. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The two items include inappropriate methods of randomization and double-blinding.

The Jadad checklist has relative merit because of its ease and simplistic approach that incorporates the most important individual components of methodological quality like randomization, blinding, and handling of patient

attrition. Allocation concealment is important because its absence has been associated with an exaggeration of treatment effects (Towheed, 2006). Because of the emphasis of quality reporting instead of actual methodological quality of the trial, Jadad is by no means perfect. To prove the reliability of quality assessment by multiple raters using the Jadad scale, Clark et al. performed a study with two groups of two independent reviewers who applied the Jadad scale to 76 randomized trials (1999). The 76 articles were randomly allocated into four groups and were reviewed during two different time periods, two months apart. The kappa statistic was used to assess inter-rater agreement which ranged from 0.37- 0.39 and improved to 0.53-0.59 with the omission of one item (Clark et al., 1999). This study also proved that there were high percentages of agreement between ratings.

Another study conducted by three surgeon raters on 2169 reports over a ten-year period showed an inter-rater agreement of 0.48 which was higher then that of the Clark, H. et al. study (Bhandari et al., 2001). After the omission of the withdrawal and dropout items it rose to 0.51-0.83. For this meta-analysis assessment of methodological quality will be graded using the Jadad Score. The grade will determine whether the article will be included in the systematic review and meta-analysis. If any article falls below a score of three on the Jadad scale, it will be immediately dropped from the review.

Cochrane Quality Assessment

The Cochrane Quality Assessment has a similar goal with the Jadad scale by testing study quality. This is the standard assessment to all Cochrane reviews.

Because of the length and nature of this assessment, the scores derived from it will not be used to exclude any articles. The scores will be compared between studies after the analysis is run. There are several ways to rate validity. One is to rate individual criteria as 'met', 'unmet', or 'unclear' and to use individual criteria like adequacy of allocation concealment in a sensitivity analyses. These criteria serve to summarize an overall assessment of how valid the results of each study are. Scales with multiple items and complex scoring systems take more time to complete than simple approaches and have not been shown to provide more reliable assessments of validity (Higgens & Green, 2005). They may carry a greater risk of confusing the quality of reporting with the validity of the study. These assessments are more likely to include criteria that do not directly measure internal validity, and are less likely to confuse reviewers. For these reasons, it is preferable to use simple approaches for assessing validity that can be fully reported.

A study conducted by Lorenzo Moja and associates assessed the methodological quality of systematic reviews (2005). In this study 965 different systematic reviews were assessed for the methodological quality. Each review data was extracted about the quality assessment of trials included in the systematic reviews. Information extracted included title, authors, type of intervention, and methods for quality assessment. These methods included scales, checklists, components studied, or composite scores, and how they planned to use the quality assessment, either as exclusion criteria or for sensitivity analysis. Of the 965 reviews, quality assessment was carried out in 88.5% of reviews, more

often in Cochrane reviews (Moja et al., 2001). This study proves that Cochrane reviews were more likely to include a quality assessment making their protocol of higher quality and their reviews less bias.

Radiographic Evidence

This meta-analysis requires that both the diagnosis and outcome (i.e., healing) be based on radiological evidence determined by a clinician or radiologist. This includes images from x-rays, CT scans, or MRI. This process was chosen because some studies use multiple different criteria and because it reduces clinician bias. For example a study reviewing the diagnosis of scaphoid fractures conclude that x-rays, computed tomography, radioisotope bone scanning, or magnetic resonance imaging along with clinical evidence from the physical examination improved the detection of fractures (Schubert, 2000). Biologically, between four and eight weeks new bone begins to bridge the fracture and can be seen on x-rays as a hard callus. This will be viewed during the outcome assessment of all studies.

Review Manager Analysis Program

There are several meta-analysis programs on the market. RevMan is the Cochrane Collaboration's program for preparing and maintaining Cochrane reviews. This study will use the version RevMan 4.2.10. RevMan not only formats a protocol for the review, but it also keeps track of all references, including ongoing studies, excluded studies, and included studies. It can perform a meta-analysis of all the data entered presenting the results visually in tables and various graphs. It is the current template used by researchers looking to publish a

Cochrane review (RevMan 2003).

Chapter 3

METHODS

A protocol was devised for the meta-analysis before retrieval of articles in order to establish inclusion criteria used in the search. A medical research specialist was consulted about search terms. The MEDLINE and CENTRAL databases were used to run the search terms. All articles received from both databases were numbered corresponding to a main hit book. The hit book is a formatted excel worksheet that contains each articles relevancy screening form outcome. Each article's title and abstract were then read and screened with the relevancy screening form by two reviewers. The relevancy screening form is a shorter version of the data extraction form that contains the minimum standard criteria that studies must have in order to be considered for the meta-analysis i.e. uses bone growth stimulators, has a control group, is a delayed or non-union fracture, and uses a healthy population.

After being assessed by the relevancy screening form, each reviewer input the corresponding article's outcome i.e. yes, no, unsure, into their individual hit book which was later transferred into the main hit book for comparison. This allowed the articles to be independently screened by two reviewers. All articles that received both yes or one unsure and one yes were then put through the data extraction screening form. If an article received two unsure ratings or one unsure and a no, a third independent review was consulted. Only one article was disputed and the third independent reviewer approved this study for inclusion. If an article received two no's, then it was excluded from the meta-analysis.

The articles that were approved for inclusion were then retrieved in their entirety and evaluated by the data extraction form. The data extraction form is a longer form that lists all criteria the study must posses to be included in the meta-analysis. It is set up into three sections: 1) Inclusion Criteria, 2) Quality Assessment, and 3) Data Extraction. Once a study made it through inclusion criteria, it was then subjected to two different quality assessments. The scores from the Jadad Quality Assessment determined whether the study was continued to data extraction. Any study that received a score less then three was excluded from the meta-analysis. The Cochrane Quality Assessment score was used in a subgroup analysis and had no affect over determination of inclusion. If a study made it through all these check points, then its data was extracted and inputted into the RevMan statistical analysis program.

Search Methods

A healthcare research librarian was consulted and the following search strategy was conducted in MEDLINE (Pubmed) and CENTRAL databases. The search was first limited to randomized controlled trials, articles published in English, human subjects, and abstracts accessible online. All articles retrieved were processed through the search strategy previously stated.

1) electric stimulation therapy OR electromagnetic fields OR electromagnetics OR magnetics

2) electric capacitive coupling

3) pulsed magnetic field*

4) (pulsed electromagnetic field*) OR pemf[tw]

5) interferential current*

6) electri* stimulation[tw]

7) #1 OR #2 OR #3 OR #4 OR #5 OR #6

8) fractures, ununited[mesh]

9) pseudoarthros*

10) fracture healing[mesh]

11) #8 OR #9 OR #10

12) fracture*[tw]

13) fractures, bone[mesh]

14) non-union[tw] OR delayed union[tw] OR un-united[tw]

15) (#12 OR #13) AND #14

16) (#11 OR #15) AND #7

17) #16 LIMITS: English, Human, Clinical Trials, Randomized Clinical Trials

Screening Process

Two reviewers independently screened and selected the studies included in the review. The use of two reviewers decreases study selection bias and sets up a confirmation system for data abstraction. A third independent reviewer was consulted on one article to adjudicate a disagreement regarding inclusion criteria. Only English language articles were used. All relevant articles found in the databases were retrieved.

Eligibility Criteria

Eligibility criterion is the bare minimum standards a study's abstract and title must meet in order to pass through the relevancy screening form. The four criteria that are addressed on the form include meeting the designated definition

of a delayed or non-union fracture, having an intervention and a control group, using a healthy population, and being a randomized or controlled clinical trial. The relevancy screening form can be viewed in Appendix B titled Meta-Analysis forms.

Definition of Delayed and Non-Union Fractures

Delayed union fractures was defined as no radiographic evidence of healing at the site after three or more months, while nonunion fractures was defined as failure to heal or evidence that the healing process has stopped after six months (Bruser & Gilbert, 1999).

Types of Control

Studies had to use a bone growth stimulator in comparison to a sham control or placebo control in order to compare the effects of the healing process. Studies that use active control modalities such as ultrasound, or surgery like bone grafts exclusively in comparison were not eligible. A sham control is an electromagnetic stimulator that is aesthetically similar to the devices used in the study, although it does not work. This device is set up to conceal from the subject and researchers which units actually work therefore leaving data unaffected by observer bias. The placebo control is another control group where subjects with similar injuries were left untreated to be used as comparisons to the intervention group. Although historically these studies have been conducted, due to the movement of human and animal rights in research, the likelihood of finding recent research with this method is low. A subgroup analysis was attempted with studies that compared bone growth stimulators to other interventions although not

enough studies were retrieved.

Healthy Population

Eligible studies had to have a healthy population with a medical diagnosis of a delayed union or nonunion fracture. Patients who had previous treatment such as bone graphs, other surgeries, or comorbidities like infection at the fractures site were eligible. Studies were not eligible if subjects had any of the following diseases: bone cancer, Insulin Receptor Substrate-1 Deficiency, aplastic anemia, osteoporosis. If the study failed to mention specifics about the population, the subjects were assumed as being healthy.

Randomized and Controlled Clinical Trials

All eligible studies had to be performed as randomized controlled trials or controlled clinical trials. Randomized controlled trials were defined as a clinical trial that includes at least one test and one control treatment where the treatments administered are allocated by a random process like a random numbers table, computer generated allocation, or by sealed envelopes. Controlled clinical trials (CCT) were defined as any study that allocates groups according to coin flips, odd-even numbers, patient social security numbers, days of the week, medical record numbers, or other such pseudo- or quasi-random processes (Higgens & Green, 2005). The reason for the distinction between the two types of studies is because CCT are deemed to have less scientific value because of limited allocation concealment. This introduces bias that randomized controlled trials do not have. The subgroup analysis looks at the affect that allocation concealment has on the combined statistical data and the results of the individual studies.

INCLUSION CRITERIA

Types of Fractures

All bone sites yielding a delayed union or nonunion fracture was used. Any type of bone fracture that resulted from acute or chronic injury was included, including stress fractures as long as they adhered to the preset definition of delayed and non-union fractures.

Radiographic Outcome and Diagnosis

Fracture diagnosis using radiographic evidence was required. The diagnosing clinician did not have to be blinded, but this criterion was recorded for further analysis between studies. The primary outcome measure also had to have radiographic evidence of a callus to declare healing of the fracture. Radiographic evidence was defined as x-ray, computed tomography, and magnetic resonance imaging.

Types of Intervention

Trials of all types of pulsed electromagnetic fields and electromagnetic stimulators, invasive or non-invasive, were included. The latter relies on direct application of an electrical field rather than induced current. Included bone growth stimulator generating units were implantable or external (Aaron et al., 2004). The definition of bone growth stimulator for this study stemmed from the FDA classification of interventions and reads, "A bone growth stimulator provides stimulation through electric and/or magnetic fields to promote osteogenesis to facilitate the healing of non-union fractures and lumbar spinal fusions. The stimulation may be delivered through capacitive coupling with

electrodes placed directly over the treatment site, or through pulsed electromagnetic fields." (FDA, 2006). Direct current bone growth stimulators were also included and was defined as direct electrical current applied by surgically-implanted electrodes with the cathode placed at the site of bone repair and the anode placed nearby on soft tissue.

Quality Assessment Procedures

We assessed the methodological quality using the Jadad score and by following guidelines from the Cochrane collaboration. Studies with a Jadad score of less then 3 were excluded. The Cochrane Quality Assessment scores were used in a subgroup analysis between studies. Both quality assessments can be viewed in Appendix A.

Data Extraction

Each reviewer independently read and reviewed the articles and completed the data extraction form. If the studies made it through both quality assessments, results were abstracted onto a data extraction form, Appendix B. The data was then entered into RevMan for analysis. If enough information were gathered, then subgroup analyses would have been performed. These subgroup analyses would have compared the differences between randomized controlled trials and controlled clinical trials, how blinding assessors affected results, and whether methodological quality affected the outcome. Because there was not enough information, sensitivity analyses were conducted instead.

The first three pages of the form detail the inclusion and exclusion criteria for the meta-analysis. If the article fulfilled all inclusion categories, then the

reviewer continued onto the fourth through sixth pages for quality assessment. If the study met the minimum score, data was extracted. The data extraction page involved the reviewer to record study specific information and results calculated from the research. This includes the number of participants, mean, and standard deviation for continuous data and dichotomous data containing total number of participants and number healed.

Exclusion Criteria

Any study that was not preformed using a randomized or quasi-randomized process, i.e. CCT, was excluded. Studies that used movement at the fracture site, a pain scale, measurements of mobility, functionality scale, or any other form of clinical diagnosis as their only outcome measure was not used. Any study that did not adhere to the definitions of delayed and nonunion fractures set by this meta-analysis was excluded. Studies that included subjects having diseases that may impede in the bone regeneration process such as bone cancer, Insulin Receptor Substrate-1 Deficiency, or aplastic anemia, was excluded. Fractures caused by medical conditions that weaken the bones, such as osteoporosis was also excluded. Studies that compared a bone growth stimulator to another modality, such as ultrasound, hormones, or surgery were not used.

Statistical Methods of Data Analysis

The statistical analysis was performed using the computer program RevMan version 4.2.10 (RevMan, 2003). The primary analysis was calculated using a random effect risk ratio with a 95% confidence level using the DerSimonian and Laird method. This method was chosen because of the lack of

data, low event rates, and small trial size. It uses a different weighting scheme dependent on the risk ratio and has better statistical properties when there are few events. A secondary analysis was conducted using a fixed effect risk ratio with the Mantel- Haenszel method. Four sensitivity analyses were conducted, omitting one article at a time, to see the affects it had on the overall analysis. Forest plots showing the confidence interval and the effect estimates for each study were generated. Each block represents a study at the point estimate of treatment effect. The horizontal line depicts the confidence interval while the area of the block indicates the weight assigned to the study in the meta-analysis (Higgens & Green, 2005). The confidence interval totals are represented by a diamond shape.

Assessment of Heterogeneity

Heterogeneity, or between study variability is described as any kind of variability between studies in a systematic review (Higgens & Green, 2005). Statistical heterogeneity is defined as variability in the treatment effects being evaluated in the different trials. Heterogeneity was addressed in this meta-analysis by using randomized and controlled clinical trials, using strict preset criteria, and adherence to the definition of delayed union, non-union, and outcome measurement. RevMan tested heterogeneity using a standard chi squared test and I^2 test. If the value from the I^2 test was > 50%, this signifies that substantial heterogeneity existed.

Since only published studies were used in this meta-analysis, publication bias is possible. Published studies generally do not represent all of the studies being performed because articles with significant or positive findings are more

likely to be published (Glasziou et al., 2001). Language bias is also a possibility since only articles published or translated in English was used. Negative studies were less likely to be found since it is known that studies without significant results are more likely to be published in non-English language journals (Higgens & Green, 2005).

CHAPTER 4

RESULTS

The primary purpose of this study was to determine the efficacy of electromagnetic bone growth stimulators on delayed and nonunion fractures. For clarity, the results section will be organized into two sections. The first section will provide a detailed review of the four included studies with article demographics and individual study methods. The second section will present the results of the meta-analysis.

Selection of Included Studies

Of the four hundred and twenty two studies that were retrieved from MEDLINE and CENTRAL, only twenty-four remained after two reviewers completed the initial relevancy screening that involved examination of the title and abstract. The complete article for each of the 24 studies were then reviewed in full by the two reviewers using strict inclusion criteria contained in the data extraction form. Twenty articles were excluded. The reasons for exclusion are summarized in Table 3. There were many articles excluded for lacking multiple criteria. The majority of articles, 26%, did not use radiographs for diagnosis or outcome. Twenty three percent of studies did not have a control group. Other reasons for exclusion were trials not randomized 22%, alternate definition of non-union 18%, other interventions used 8%, and use of at risk subjects 3%. The Final Relevancy Screening Form of Table 2 details the results from the data extraction form. The two reviewers disagreed on one article, which was examined by a third reviewer and was found to meet inclusion criteria. Four

studies therefore met all inclusion criteria and data was extracted for the meta-analysis. This criteria consisted of randomization, definition of injury, healthy population, radiographic diagnosis and outcome, and a control group. These studies include *Pulsed Magnetic Field Therapy for Tibial Non-union* (Barker, Dixon, Sharrard, & Sutcliffe, 1984), *A Double-Blind Trial of Pulsed Electromagnetic Fields for Delayed Union of Tibial Fractures* (Sharrard, 1990), *A Prospect Double-Blind Trial of Electrical Capacitive Coupling in the Treatment of Non-Union of Long Bones* (Scott & King, 1994), and *Electrical Treatment of Tibial Non-Union: A Prospective, Randomised, Double-blind Trial* (Simonis, Parnell, Ray, & Peacock, 2003).

Detailed Review: Article Demographics

The four studies included a total of one hundred and sixteen subjects. In Barker's study, published in 1984, sixteen subjects were used with an age range from 19-72 years with a mean age of 34.4. All subjects were healthy and with fractures that had not healed for at least a year making them non-unions. Nine subjects were randomly allocated to an active stimulator while seven others received a sham unit. The mean age of the intervention group was 38 years while the mean age of the control group was 29.9 years.

In the study by Sharrard, forty-five patients were included in the trial, twenty were randomly assigned to active units while twenty-five were randomly assigned to receive sham controlled units. Only fractures at the site of the tibia were included in this study. The age range of the study was 18-84 years; the mean age of the active group was 34.7 years and for the control group it was 45.4.

Scott and King's study contained twenty-one subjects, ten allocated to the active group and eleven to the control group. The age of the subjects ranged from 23-87 years. The average age of the active group was 39.6 years compared to 45.8 years for the control group. In the Simonis study which included thirty-four tibial fractures, the age range of subjects was 16-61 years with the mean age of 32 years (2003). Eighteen subjects were randomly allocated to the active group while sixteen were given dummy units for the control group.

Every article was evaluated with two different quality assessment measures, the Jadad Scale and Cochrane Quality Assessment (Appendix A). Table 4 compares each studies scores against their meta-analysis weighting. The Jadad Quality Assessment is a simple five question scale that measures study design and reporting quality with a numerical score from 0-5, with zero being the weakest and five being the strongest (Jadad, 1996). No study was excluded because of their Jadad Quality Assessment score. Simonis study was the only one with a perfect score of 5. Both Barker and Scott received ratings of 4.5 with Sharrard trailing with a score of four. All these scores indicate that the four studies were high quality, however these Jadad ratings differed vastly from the Cochrane Quality Assessment scores. The Cochrane Quality Assessment is similar to the Jadad scale but is a longer form using twelve questions. Answers are given a numeric value based on its scientific strength with the highest possible score being 24 (2 points per question). Scotts study received the top score of 22.4. Barker's study followed with a score of 21.1. Simonis study received the lowest rating, 18.3.

Detailed Review: Individual Study Methods

The Barker study included only tibial non-unions (Barker et. al. 1984). The electromagnetic bone growth stimulators used were developed by Bassett and used coils that fit around the cast of each patient. The active machines produced a 1.5 mT peak, 5 ms burst waveform and repeated at 15 Hz. The dummy machine for the control group differed from the active one by an internal connection which diverted their output to an internal load thus ensuring that no electromagnetic stimulation occurred. Both machines housed a concealed clock to check the compliance of each patient with the treatment protocol. Other clinical protocols included immobilization with a full leg plaster cast, non-weight bearing activity, and clinical examinations every 12 weeks. All staff remained unaware of which type of machines patients were allocated to for the full 24 week duration of the study.

In the study conducted by Sharrard all subjects were diagnosed with a delayed union of the tibial shaft. The 45 cases were enrolled from sixteen study centers using strict admission criteria. Similar to the previous study, all subjects were fitted with a full-leg plaster cast with their knee flexed at 20-30 degrees. They were given either an active or sham stimulator which were indistinguishable in appearance thus blinding was maintained for both the patient and the doctor. The unit consisted of copper wire coils positioned on the cast adjacent to the fractures site in a Helmholtz configuration. The signal used for the pulsed electromagnetic stimulation was a quasi-rectangular form set at 15 Hz bursts of 20 individual pulses. The patient was instructed to bear no weight on the extremity

and to use the unit for 12 hours per day for a period of 12 weeks.

Thirty-four patients with tibial non-unions were allocated into two treatment groups during Simonis study . All patients received a unilateral external fixator with compression. The patients in the active group received a pulsed electrical current from two large external coils placed over the fractures site. The coils were attached by telescopic rods so they would be in direct contact with the skin over the non-union site and were positioned with a crepe bandage. The pulse had a 3 ms duration in intervals of 40 ms with a peak current of 6 A at 150 V passing through the active coils. The electrical device used in the dummy group was similar in appearance and was also applied around the fracture site. However, this device only passed a current into a small secondary coil which was not in contact with the leg. No current was passed through the two larger coils around the fractures site. All study personal were blinded to the assignment status of each case until the conclusion of the trial. The patients were instructed to use the devices fourteen hours per day for six months. Each device was outfitted with a hidden timer to check patient compliance.

In the study performed by Scott patients were randomly assigned to receive either an unmodified Orthopak bone-growth stimulator or a modified device which gave no electrical output for the placebo group. Every patient was managed with a plaster cast or brace with openings for the electrical stimulator to be placed on the skin surface. The active units delivered a five to ten volt peak sine wave at 60 kHz. All units were indistinguishable and were monitored by clinicians during the patient's visits with the dummy units giving the same signals

as the active units upon daily check of the battery. Blinding for both patients and physicians was maintained until the conclusion of the study. Since most of the patients had previously been encouraged by their doctors to bear weight on the extremity before entering the study, the protocol continued to allow weight bearing while using the bone growth stimulator. Clinical evaluations were performed every three months.

All four studies were labeled as randomized clinical trials, but only one study (Simonis) described specifically how the randomization occurred i.e. electromagnetic units were assigned from a randomized predetermined list. The study did not describe how the list was generated, e.g. computer generated, however, the study did describe the allocation concealment process which was done by an independent member of the hospital not involved with the study who was responsible for randomly assigning the machines and kept the randomization scheme secure until completion of the trial (Simonis, Parnell, Ray, & Peacock, 2003). The only other article that described details of the randomization scheme was Barker who described randomizing units by a stratified randomization procedure. The article did not define the specific factors used in the stratification however (Barker, Dixon, Sharrard, & Sutcliffe, 1984).

Every study stated that it maintained a blinded assessment of outcomes. Two studies, Sharrard and Barker, used separate doctors not involved with the study or managing patients to read the radiographs and determine outcomes. The other two studies, Scott and Simonis, used the same staff involved in treatment and follow up to assess outcomes in the subjects but both articles stated the staff

were blinded to treatment assignment (i.e. the codes were not broken until the end of the study). Between articles there were also differences in the research methods employed that divided the studies into the two groups. The Scott and Simonis studies whose own researchers judged the radiographs had comparatively more healing in the control subjects 14/23 (60.8%) compared to 1/36 (3%) in the other two studies that employed independent clinicians. These results could be from the lack of truly independent assessors, but are more likely from the different criteria for defining healing.

Treatment protocols and duration of therapy varied over the four studies. In the study conducted by Simonis, subjects were treated for a maximum of six months (Simonis, Parnell, Ray, & Peacock, 2003). At monthly evaluations radiographs were taken. If union had occurred, stimulation was stopped and the patient was graduated to weight bearing with an orthoplast gaiter. With Scotts study any patient whose non-union healed within six months was withdrawn from treatment and was monitored until the end of the period. If a non-union was still healing at the six month mark, the treatment was continued up to nine months (Scott & King, 1994). The maximum duration of treatment for Barkers study was one year (Barker, Dixon, Sharrard, & Sutcliffe, 1984). For the first six months the patients were casted and used the bone growth stimulator. Evaluations were made every six weeks. The patients were kept casted and stimulation continued for the six months even if union occurred in prior weeks. Sharrard patients received treatment for three months (Sharrard, 1990). No evaluations were made until the end of the three month period. The patients had the ability to opt out the

trial and would not be included in the study.

Even though inclusion criteria consisted of radiographic diagnosis and outcome, each articles definition of healing differed slightly. Sharrard and Scott used clinical assessments along with the radiograph to define union. These assessments included measuring mobility of the fracture with a goniometer, a visual analogue pain scale, and rating of discharge if an infection was present. A non-union was defined as healing if there was less pain, less motion at the site of fracture, and a definite increase of callus and trabecular bridging radiographically in comparison to findings at the previous visit. Barker's study also used clinical examinations along with stress radiographs to define union. If both observers where unable to detect movement on imaging when the tibia was stressed, then the fracture was defined as clinically united. Simonis based their definition of healing strictly on three radiological signs, loss of distinction at the fracture gap, cortical bridging, and trabecular bridging. No clinical assessments were taken. These differences could contribute to between study variability. By choosing the criteria of radiograph diagnosis inter-clinician differences was introduced. There is a possibility of detection bias with the variability of clinicians and their diagnostic experience reading the radiograph and evaluating clinical signs of fracture healing.

Meta-analysis Results

All results were input as dichotomous data (i.e., intervention (intervention vs. control) and healed (yes vs. no)). Table 5 is a summary of the meta-analysis results using a random effect and fixed effect model. It also includes the results

of the sensitivity analyses where each individual study was removed and the results re-calculated. Each sensitivity analysis was calculated using the random effect model.

The primary finding of the meta-analysis was a summary random effect risk ratio of 2.62, with a 95% confidence interval of 0.78 to 8.78. The Z statistic test of the overall effect and was 1.57 (P=0.12). Figure 1 displays the forest plot of the meta-analysis based on the random effects model. It shows the percentage weight assigned to each study in the analysis and includes their individual risk ratios and confidence intervals.

There was significant heterogeneity between the results of the four studies. The test of homogeneity was highly significant (Chi^2=21.91, 3 d.f., p < 0.0001) and the I^2 statistic showed substantial between study variability (86.3%). Out of the four studies, only Barker's favored the control over treatment (RR=0.91). The other three studies all favored the intervention group but the RR estimates varied substantially from 1.78 to 14.18.(fig 1)

A secondary analysis using the fixed effect method is shown in Figure 2. The summary fixed effect risk ratio was calculated at 2.36, 95% CI 1.57 to 3.53 with a Z score of 4.16 (P<0.0001). The fixed effect analysis results in substantial changes in the weights given to the individual studies when compared to the random effect model. This is expected as the weights calculated in the fixed effect method include only with-in study variability and are based only on the sample sizes of the individual studies, whereas the random effect model includes an additional term for the between study variability Despite the overall

statistically significant summary RR with the fixed effect analysis there was again significant between study heterogeneity. The test of homogeneity was Chi^2 =21.9, 3 d.f., p<0.0001), and the I^2 statistic again showed substantial between study variability (86.3%).

Subgroup Analyses

Initially it was planned to run three separate subgroup analyses addressing the differences between randomized and controlled clinical trials, the blinding of outcome assessors, and methodological quality. Since only four studies ended up being included in the analysis, there was not sufficient information to run these subgroup analyses.

Sensitivity Analyses

In order to examine how much the overall meta-analysis results were influenced by each individual study we undertook a sensitivity analysis in which each study was dropped and the analysis was repeated. The first sensitivity analysis dropped Barker's study leaving 100 study subjects from the other three studies. This study was given a 34.67% weight in the original analysis and had a risk ratio of 0.91. After removing this study the risk ratio increased to 5.48 with a non-significant 95% CI 0.72 to 41.48 (Z score=1.65, P=0.10). The tests for heterogeneity (Chi^2=8.55 2 d.f., P=0.01) and I^2=76.6% again revealed significant heterogeneity. After dropping Barker's study this sensitivity analysis has the highest risk ratio which suggests a much higher healing rate with bone growth stimulators. However the presence of heterogeneity means that this summary estimate should be interpreted with caution..

The second sensitivity analysis dropped Sharrard's study. In the original meta-analysis this study heavily favored the bone growth stimulator. Individually this study had a 12.50 risk ratio and was weighted 18.53% of the overall meta-analysis. After removing this study the sensitivity analysis had 77 subjects. The risk ratio decreased to 1.62 with a 95% CI 0.06 to 4.33 (Z score= 0.96, P= 0.34). Heterogeneity was calculated as (Chi^2=10.37, 2 d.f., P=0.006,) and I^2=80.7%. This analysis had the lowest risk ratio of the four but also a smallest confidence interval making the RR value more precise. We can conclude that there is little effect of healing from bone growth stimulators. Although this analysis shows moderate heterogeneity.

In the meta-analysis Scott's study favored the bone growth stimulator with a risk ratio of 14.18 and was weighted 12.58%. Once removed the sensitivity analysis had 95 participants, the risk ratio decreased to 1.94 with a 95% CI 0.63 to 5.92 (Z=1.16, P=0.25). Heterogeneity was calculated (Chi^2=14.83, 2 d.f., P=0.0006), and I^2=86.5%. This analysis shows little benefit of healing from bone growth stimulators.

The last sensitivity analysis dropped Simonis study. The study contributed 34.23% weight to the meta-analysis with a risk ratio of 1.78. This sensitivity analysis had 82 participants and the calculated risk ratio increased to 4.99 with a CI 0.13 to 190.28 (Z=0.86, P=0.39). Heterogeneity was calculated (Chi^2=28.45, 2 d.f., P<0.00001) and I^2=93.0%. This analysis had the second largest risk ratio suggesting a healing effect from the bone growth stimulator but it also had an exceedingly wide confidence interval and highest heterogeneity

nullifying the conclusion.

CHAPTER 5

DISCUSSION

Statistical Findings

Since the meta-analysis included only four studies, I chose to vary the statistics in order to gain more insight into the effect of bone growth stimulators. Both the fixed effect and random effect methods are presented because one proved statistically significant while the other did not. The meta-analysis uses the random effects risk ratio for its primary findings because this method is more conservative with wider confidence intervals. The random effects meta-analysis showed a non-significant risk ratio of 2.62 (95% CI= 0.78-8.78 p=0.12). The random effects method assumes that each study is a sample from a larger population of studies, and takes into account between-study variability. The study specific weights are more evenly balanced in a random effects model compared to the fixed effects model.

Although this meta-analysis was not statistically significant, the summary point estimate did find that fracture healing was 2.62 times more likely with a bone growth stimulator than without. Limitations of the study include small number of studies each with a sample size and significant heterogeneity. Because of these limitations the summary findings need to be interpreted with extreme caution.

There are many reasons why significant heterogeneity was present in the meta-analysis. This can be attributed to the various methodology across studies. First, the varying protocols used in the different studies may have contributed to

study-to-study variability. We cannot be certain whether the unit itself or the additional protocols (termed cointerventions) facilitated healing of the fractures. For instance in the Simonis study, their patients were advised to be strictly non-weight bearing while the Barker and Sharrard studies immobilized patients by placing them in a long leg plaster cast. This differed in the Scott study where they allowed weight bearing: they reported, "Similarly, even when we considered that a period of non-weight bearing was advisable at the beginning of capacitive coupling, this judgment was not enforced. Most of the patients had previously been encouraged to bear weight on the extremity, and we thought it inappropriate to change this behavior because of the risk of introducing an additional variable." (Scott & King, 1994).

Other variations in study methods include different lengths of follow-up. For example, Sharrard followed his subjects for only three months while the duration other studies lasted for nine months up to a year. Every study used a different bone growth stimulator unit with varying duration and dosage. Simonis was the only study to assess bone growth stimulators on other long bones besides the tibia.

In his discussion, Sharrard mentions the wide spectrum of bone and soft tissue injury that may occur. The different injuries sustained by individual subjects can vary between simple and severely displaced fractures where simple fractures do not need supplemental aid to achieve union. Sharrard also commented that his two treatment groups differed significantly in age distribution. When looking at the statistics, Simonis and Barkers studies have

more frequent healing rates in the control group. Simonis treatment groups had an imbalance of prior operations with the control group having 11 operations prior to the study. Barker contributed the high healing rate in their control group to the fact that the additional protocol resulted in long term immobilization and non-weight bearing. He comments that because of the amount of time the control group was required to use the unit, it further reduced the amount of limited activity on the affected limb which then promoted healing.

There were important differences in baseline healing rates between studies. In the Sharrard and Scott studies only a minority of the control group healed i.e. 4% and 0% respectively. In comparison in the Simonis study where half healed and 85% of Barker's control group. This can be explained by Barker having the longest duration of treatment of one year compared to Sharrard and Scott with three and nine months. When reducing Barker's duration of treatment, at three months the study had only a 28% healing rate.

It is also interesting comparing publication between the four articles. Two studies, Sharrard's and Scotts, were published from The Journal of Bone and Joint Surgery. Barkers was published in Lancet and the Simonis study was in Injury. This is relevant because this could signify publication bias where journals only publish studies with significant findings. Both Sharrard and Scott's studies were published in the same journal with results that suggest a beneficial effect of bone growth stimulators.

Comparison of Random Effect and Fixed Effects Methods

The random effect and fixed effect model analyses generate different

results primarily because of the differently ways the two methods calculate study variance. Both meta-analyses use the same studies although their contributing weights are significantly different which results in dissimilar risk ratios, Z scores, and P values. The primary difference between the two is the inclusion of between study variance in the random effect model.

In RevMan the calculated study weights are dependent on both the sample size and the event rate. Because estimations are more precise when there are more events, trials with high event rates get weighted more. This explains why the Barker study, that has the least amount of participants but the largest healing rates (i.e. events) was given heavy weighting. At the other extreme, a trial with little or no even rates gets little or no weight. This is illustrated by the Scott study which is given the least weight in both meta-analyses because of the control group having no events.

The weighted averages differ between statistical methods because of how the mathematical models interpret standard error, confidence intervals, and variance. The Mantel-Haenszel method operates by giving studies with less variance, or standard error, more weight while assuming that every study is evaluating a common treatment affect. The DerSirmonian and Laird or random effects method does not assume that only one treatment effect exists, i.e. bone growth stimulator. This method factors in other variables and estimates the mean and standard deviation of different effects when giving the risk ratio.

The fixed effect method seen in Figure 2 estimates study specific weight only on the basis of the size of each study i.e. within study variability. The fixed

effect analysis weighted the four studies very differently from the random effects model for example it significantly reduced the weight of the Sharrard and Scott study from 31.11% to 8.24%.

Importance of Between Study Heterogeneity

Despite the debate as to whether the results are statistically significant or not, both meta-analyses show considerable heterogeneity. Even though the meta-analysis was set up with strict criterion for scientifically sound results, there were still major differences between studies that we could not control for. These differences included patient selection factors, design of bone growth stimulator units, dosage and duration of treatment, differences in the definition of healing, use of adjunct protocols with the units, patient compliance, and time between follow up appointments. All of which could have contributed to the differences in outcome between studies.

Most of the four articles did not address the problem of patient compliance with the bone growth stimulator unit. Because the intervention is marketed as a portable unit and results are dependent on patient use over a prolonged period of time, results can be affected from inadequate instructions or non-compliance. Two studies used a concealed clock that recorded the activity of the stimulator (Barker, Dixon, Sharrard, & Sutcliffe, 1984, Simonis, Parnell, Ray, & Peacock, 2003). One patient from the control group of Barkers study was non-compliant with treatment protocol and dropped from the study. All subjects from Simonis adhered to protocol. In Scotts study the devices issued a readout that showed the number of days of usage to assess compliance. Although the unit could not record

the duration of each use. One patient from each group were excluded due to failure to comply with the use of device. The units in Sharrard's study could not monitor patient compliance although it was found that one patient tampered with his device and broke the code dropping him from the study.

Another source of between study variability was the fact that one study included different fracture sites. Barkers, Simonis, and Sharrard's articles designated tibial fractures as inclusion criteria while Scott's study researched the effect on other long bones (Scott & King, 1994). Nineteen percent of fractures in Scotts study were on the femur while 9% were ulnar fractures. The majority of fractures, 71% occurred over various sites on the tibia. This introduces heterogeneity because some bones are innervated with a bigger blood supply then others, thus allowing more chance to heal.

Meta-analysis Methods

The main purpose of this study was to evaluate the efficacy of bone growth stimulators on delayed and nonunion fractures using randomized controlled trial design. This research question proved to be a difficult one to evaluate because of the small number of highly variable studies published on the subject. Out of the twenty-four articles that made it through the initial screening, only four met final inclusion criteria which included RCT or CCT, definition of injury, healthy population, radiographic diagnosis of injury, comparison against a bone growth stimulator, and a control group . The majority of studies were excluded because there was no radiographic outcome or diagnosis and many studies did not have a control group. Even when we adjusted the inclusion

criteria to include only randomized studies with a control group we found only an additional 5 studies. After reviewing the articles there was not a significant amount to run another separate meta-analyses.

A subgroup analyses was planned to compare the bone growth stimulator to alternate modalities like surgery or ultrasound. Only five out of the twenty four articles addressed this issue and so there were not enough to warrant a subgroup analysis. In hindsight only two arm trial studies with a control group were included. Many studies were excluded because they did not include a control group of subjects whose fractures would receive no interventions to heal.

Limitations of Inclusion Criteria

Only four out of the twenty-four studies passed the data extraction form. The main reason why most studies did not make it to data extraction is because they did not have a diagnosis or outcome radiograph identifying healed fractures. Seventeen out of the twenty articles did not specify how the diagnosis was made or used clinical tests to prove healing. Even if this criterion was eliminated, twelve out of these seventeen studies had no control group or randomization, two important criteria that cannot be omitted. These articles got past the initial relevancy screening with abstracts that stated they were randomized controlled trials, but after retrieving and reading the full article, they did not meet the definition of a randomized trial. Of the other five studies that were excluded from the meta-analysis, none of them met the definition of delayed and non-union fractures. These studies used acute fractures and subjects with osteoarthritis, two extremely different injuries with prognoses that are documented to more easily

return to healing without intervention. They also used other controls included surgery, osteogenic proteins, or ultrasound. Because there are many restrictions on human research, experiments with a sham or control where subjects are not guaranteed to get a treatment are getting harder to conduct or find. To run another study by adjusting any one of these criteria would be accepting articles that no longer addressed the initial research question.

Comparison by Quality Assessment

When establishing the methods there were two forms used for quality assessment. The Jadad score, a table of five items with scores ranging from zero to five, were calculated. Any study with a score less then three was excluded from the meta-analysis. Only one study, *Electrical Treatment of Tibial Non-Union: A Prospective, Randomised, Double-Blind Trial,* received a perfect score of five while the rest of the studies received 4.5 or 4 (Simonis, Parnell, Ray, & Peacock, 2003). Since the initial inclusion criterion for the meta-analysis were strict, every study that made it through the initial criterion passed the Jadad quality assessment. The Cochrane Quality assessment tool was added to ensure the methodological quality of the included articles. No studies were excluded because of their scores.

Randomized Trials versus Controlled Clinical Trails

The difference between a randomized controlled trial and a controlled clinical trial was that the former uses a formal randomization scheme generated from a computer or a random numbers table while the latter uses a non-randomized or quasi-random process such as organizing groups according to date

of birth or social security number. All four articles included in this analysis were designated as randomized controlled trials. Only one article, *Electrical Treatment of Tibial Non-Union: A Prospective, Randomized, Double-blind Trial,* was randomized by allocating the coded electromagnet units from a randomized predetermined list. (Simonis, Parnell, Ray, & Peacock, 2003). Barkers study used a minimization procedure of randomization to keep the groups as even as possible (Barker, Dixon, Sharrard, & Sutcliffe, 1984) Sharrard and Scotts studies stated that the study was randomized, but they did not reveal the procedure as to how. We cannot know if they were truly randomized because the methods of random assignment were not revealed. This is why randomized and controlled clinical trials were included in the meta-analysis in order to keep any articles that may be quasi-randomized.

It is important for studies to address allocation concealment or randomization will be lost and bias will be introduced. If the allocation of units are not concealed then researchers can deduce the subjects grouping despite randomization and preferential treatment can be given. Scotts study kept allocation concealment by stating that the manufacturer who kept the randomization code took no part in allocating the units to patients, nor was he involved in the study or informed of the outcomes after the code was broken. At the end of the study, the researchers tested the units to ensure the information was correct. Barkers study did not state measures to keep allocation concealment, but multiple times declared that all staff were unaware of the machine type during the study.

Blinding Outcome Assessors

Another research question posed at the beginning of the study asked if the blinding of outcome assessors affect the result. One article stated that the junior member involved in patient care also performed clinical outcome tests that were used for outcome diagnosis (Scott & King, 1994). This would be a clear example of bias if the assessor was not blinded. None of the four articles reported a lapse in blinding for any of their trials.

Conclusion

This meta-analysis was limited by the small number of trials which were highly variable in their design. Based on the data available there is insufficient evidence to support the use of bone growth stimulators for nonunion fractures. Most studies identified either were not randomized, had poor methodology, or used bone growth stimulators for other means.

With the abundance of evidence on direct stimulation with spinal surgery it would be easy to run a meta-analysis on this subject. Another more accessible way to research bone growth stimulators would be comparing its affects on acute fractures. Since many acute fractures are known to heal on their own, you could ethically use a control group for comparison to retain scientific integrity. Besides a sports medicine setting where athletes do not have the luxury of time for their fractures to become delayed or non-unions, it would not be clinically relevant to the general populations. But the results of such a study could give insight to the effects of healing bone growth stimulators to aid the healing of fractures. In conclusion I encourage and urge researchers to run more scientifically sound

studies in order to advance the uncharted technology and usage of electromagnetic bone growth stimulators.

Table 1 Comparisons of Meta-Analyses using Electromagnetic Field Stimulation

Citation	Specifications	Intervention	Statistics/Analysis	Results	Limitations
Electromagnetic Field stimulation for the treatment of delayed union or non-union of long bones By: Punt, B., den Hoed, P., & Stijnen, T. (2004)	-only researched on long bones (tibia, fibula, femur, humerus, radius, ulna)	-PEMF -EMF -pulsed and non pulsed	-REVMAN program used -Relative Risk for dichotomous data -Mean difference for continuous data -95% confidence interval -Chi squared test for heterogeneity	-Study currently being conducted	N/A
Electric stimulation and hyperbaric oxygen therapy in the treatment of nonunions By: Karamitros, A., Kalentzos, V., & Soucacos, P. (2006)	-used electric stimulation in combination with other therapy (hyperbaric oxygen)	-PEMF -Direct Current -Capacitive coupling -hyperbaric chambers	N/A	N/A	-only a review, not a meta analysis -does not show the efficacy of PEMF by itself

Table 1 (Cont.)

Effect of Electric Stimulation on Musculoskeletal Systems: A Meta-Analysis of Controlled Clinical Trials By: Akai, M. & Hayashi, K. (2002)	-used articles from 1966-1999 -study tests the efficacy of PEMF on bones and for soft tissue/ joints -pooled only part of data b/c heterogeneity -mask reviewers during data and results extraction	-PEMF	-ROMA 88 program used -DerSimonian and Laird Method -pooled rate difference with random effect models -95% confidence interval -quality criterion by Sackett	-12 out of 20 studies reviewed on bones -16 out of 29 studies reviewed on soft tissue/jt -trials show no proof that PEMF has specific effect on health -Positive findings when used on tissue repair	-wide distribution of types of injuries -various types of outcome assessments -difficulty finding primary endpoints in each study -limited studies included in review -time gap exists on current studies -did not disclose statistical results from ROMA 88

Table 2 Final Relevancy Screening Form
Included Articles

Title	*Author*	*BGS Total*	*BGS Healed*	*Control Group Total*	*Control Group Healed*
A prospective, double-blind trial of electrical capacitive coupling in the treatment of non-union of long bones	Scott, G et. Al	10	6	11	0
Pulsed magnetic field therapy for tibial non-union. Interim results of a double-blind trial	Barker, AT et. Al	9	7	7	6
Electrical Treatment of tibial non-union: a prospective, randomized double-blind trial	Simonis, RB, et. Al	18	16	16	8
A double-blind trial of pulsed electromagnetic fields for delayed union of tibial fractures	Sharrard, WJ	20	10	25	1

Table 2 Final Relevancy Screening Form - Excluded Articles (Cont.)

Title	*Author*	*Reasons for Exclusion*
Implantable direct current stimulation in para-axial cervical arthrodesis	Welch, WC et. Al	Trial type, surgery used, no control, randomization, no radiograph diagnosis, fresh fractures
Pseudarthrosis after lumbar spine fusion: nonoperative salvage with PEMF	Simmons, JW Jr., et. Al	No control group, multicenter trial, no outcome radiograph, not randomized
Treatment of nonunions of long bone fractures with shock waves	Wang, CJ et. Al	Not randomized, no control group, use of surgery, use of pain scale
High-energy extracorporeal shock wave treatment of nonunions	Rompe, JD et. Al	No control group, not randomized, no radiograph for diagnosis, no BGS used
Pulsed electromagnetic fields for the treatment of bone fractures	Satter Syed, A et. Al	Not randomized, no control group, def of delayed union, no diagnosis by radiograph
A model for the prediction of time to union in fractures of the tibia	Fourie, JA et. Al	Use of interferential currents, not relevant to study, no radiograph diagnosis/outcome, not randomized
Stimulation of bone healing in new fractures of the tibial shaft using interferential currents	Fourie, JA et. Al	Use of interferential currents, no radiograph diagnosis, use of fresh fractures
Tibial nonunion treated with DC, capacitive coupling, or bone graft	Brighton, CT et. Al	Not randomized, no control group, bone graft use, no outcome radiograph
Use of capacitive coupled electric fields in stress fractures in athletes	Benazzo, F et. Al	No control group, not randomized/trial type, use of stress fractures, no outcome radiograph
A double-blind trial of the clinical effects of pulsed electromagnetic fields in osteoarthritis	Trock, DH et. Al	Use of osteoarthristis, no radiograph outcome
Pulsed electromagnetic fields for the treatment of bone fractures	Satter Syed, A et. Al	No control group, def of delayed union, not randomized

Table 2 (Cont.)

Title	*Author*	***Reasons for Exclusion***
A multicenter study of the treatment of non-union with constant direct current	Brighton, CT et. Al	No control group, def of nonunion, no outcome radiograph
Effects of differentiated stress stimuli and electromagnetic fields on bones	Ziegenfelder, T et Al	Not in English
The effects of extracorporeal shockwave on acute high-energy long bone fractures of the lower extremity	Wang et. Al	No radiograph for inclusion, use of pain scale, surgery, other intervention for control
Implantable electrical bone stimulation for arthrodeses of the foot and ankle in high risk patients: a multicenter study	Saxena, A et. Al	No radiograph for inclusion, used surgery, retrospective, no control group
Prospective comparison of the effect of DC electrical stimulation and PEMF on instrumented posterolateral lumbar arthrodesis	Jenis, LG et. Al	Use fresh fractures, no radiograph diagnosis
The use of implantable DC stimulation in multilevel spinal fusion without instrumentation. A prospective clinical and radiographic evaluation with long-term follow-up	Tejano, NA et. Al	Not randomized, no control group, def of injury, no radiograph diagnosis
A ten-year review of treatment of delayed union and nonunion with an implanted bone growth stimulator	Cundy, PJ et. Al	No control group, not randomized
Treatment of non-union by pulsing electromagnetic field: European multicenter study of 308 cases	Hinsenkamp, M et. Al	Multicenter study, no control group, def of nonunion, no radiograph diagnosis healing, no pop. Reg.
Effects of differentiated stimuli caused by putting weight and electromagnetic fields on bones	Ziegenfelder, T et. Al	Not delayed or nonunion fractures, not randomized, no control group
Pulsed electromagnetic field treatment failure in radius non-united fracture healing	Madronero, A et. Al	Not randomized, no control group, no radiograph diagnosis

Table 3 Reasons for Article Exclusion

1) Use of at risk subjects.....2 studies
2) No control group.....15 studies
3) Experiment not randomized.....14 studies
4) No radiographic diagnosis or outcome.....17 studies
5) Does not conform to definition of delayed or non-union fractures.....12 studies
6) Other intervention used.....5 studies

Table 4 Quality Assessment Comparison

Study	***Jadad Score (5)***	***Cochrane Score (24)***
Barker- *Pulsed Magnetic Field Therapy for Tibial Non-Union*	4.5	21.1
Scott- *A Prospective, Double-Blind Trial of Electrical Capacitive coupling in the Treatment of Non-Union of Long Bones*	4.5	22.4
Sharrard- *A Double-Blind Trial of Pulsed Electromagnetic Fields for Delayed Union of Tibial Fractures*	4	20.8
Simonis- *Electrical Treatment of Tibial Non-Union: A Prospective, Randomised, Double-Blind Trial*	5	18.3

Table 5 Meta-analysis Statistical Results

Comparison or outcome	Studies	Participants	Statistical method	Effect size
01 Electromagnetic Stimulation vs. Control				
01 Fixed Effect RR	4	116	RR (fixed), 95% CI	2.36 [1.57, 3.53]
02 Random Effect RR	4	116	RR (random), 95% CI	2.62 [0.78, 8.78]
03 Sensitivity Analysis (Drop Barker)	3	100	RR (random), 95% CI	5.48 [0.72, 41.48]
04 Sensitivity Analysis (Drop Sharrard)	3	71	RR (random), 95% CI	1.62 [0.60, 4.33]
05 Sensitivity Analysis (Drop Scott)	3	95	RR (random), 95% CI	1.94 [0.63, 5.92]
06 Sensitivity Analysis (Drop Simonis)	3	82	RR (random), 95% CI	4.99 [0.13, 190.28]

Figure 1 Random Effects Anlaysis Risk Ratio

Review: Efficacy of Electromagnetic Bone Growth Stimulators on Delayed Union and Non Union Fractures
Comparison: 01 Electromagnetic Stimulation vs. Sham Control
Outcome: 04 Random Effect RR Analysis

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Barker	7/9	6/7		34.67	0.91 [0.57, 1.44]
Sharrard	10/20	1/25		18.53	12.50 [1.74, 89.61]
Scott	6/10	0/11		12.58	14.18 [0.90, 223.54]
Simonis, Par	16/18	8/16		34.23	1.78 [1.06, 2.98]
	57	59			
Total (95% CI)				100.00	2.62 [0.78, 8.781

Total events: 39 (Treatment), 15 (Control)
Test for heterogeneity: Chi^2=21.91, df=3 (P<0.0001), I^2=86.3%
Test for overall effect: Z= 1.57 (P=0.12)

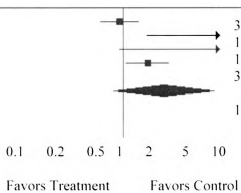


Figure 2 Fixed Effects Analysis Risk Ratio

Review: Efficacy of Electromagnetic Bone Growth Stimulators on Delayed Union and Non Union Fractures
Comparison: 01 Electromagnetic Stimulation vs. Sham Control
Outcome: 03 Fixed Effect RR Analysis

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (random) 95% CI
Barker	7/9	6/7		40.69	0.91 [0.57, 1.44]
Sharrard	10/20	1/25		5.36	12.50 [1.74, 89.61]
Scott	6/10	0/11		2.88	14.18 [0.90, 223.54]
Simonis, Par	16/18	8/16		51.07	1.78 [1.06, 2.98]
	57	59			
Total (95% CI)				100.00	2.36 [1.57, 3.53]

Total events: 39 (Treatment), 15 (Control)
Test for heterogeneity: Chi^2 =21.91, df=3 (P<0.0001), I^2=86.3%
Test for overall effect: Z= 4.16 (P<0.0001))

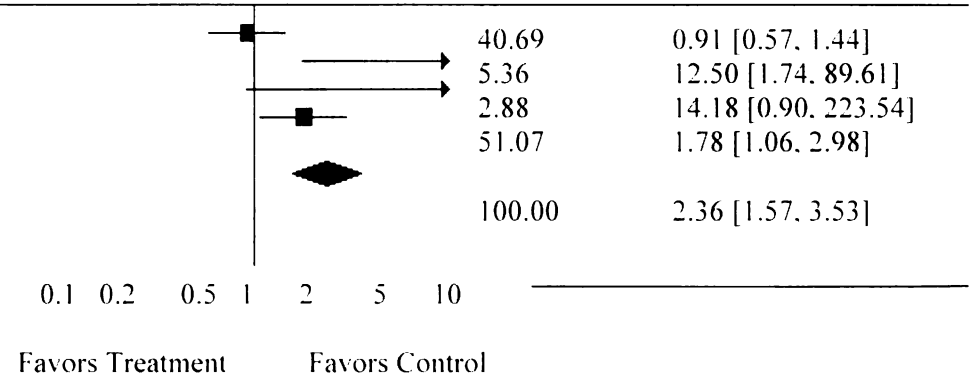


Figure 3 Sensitivity Analysis Drop Barker

Review: Efficacy of Electromagnetic Bone Growth Stimulators on Delayed Union and Non Union Fractures
Comparison: 01 Electromagnetic Stimulation vs. Sham Control
Outcome: 03 Sensitivity Analysis (Drop Barker)

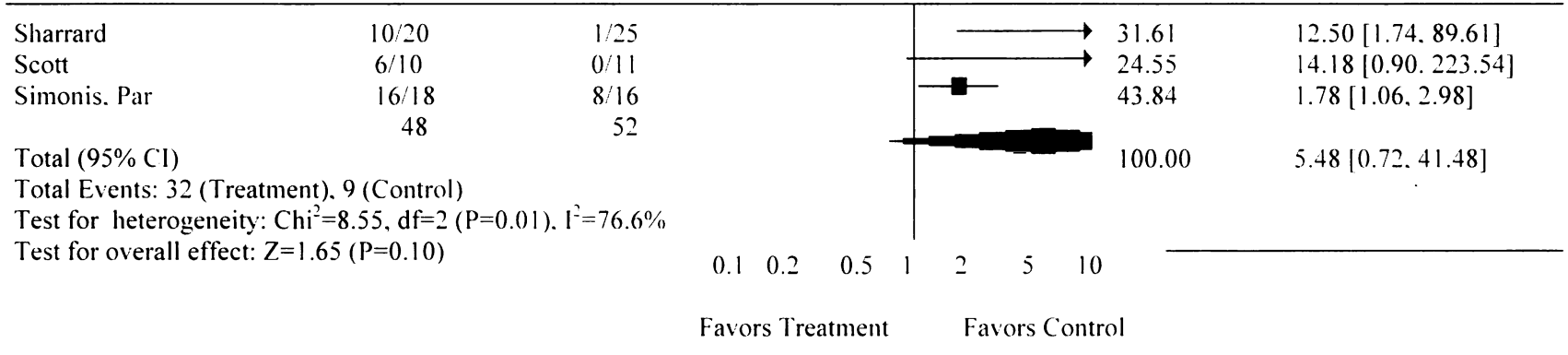


Figure 4 Sensitivity Analysis Drop Scott

Review: Efficacy of Electromagnetic Bone Growth Stimulators on Delayed Union and Non Union Fractures
Comparison: 01 Electromagnetic Stimulation vs. Sham Control
Outcome: 05 Sensitivity Analysis (Drop Scott)

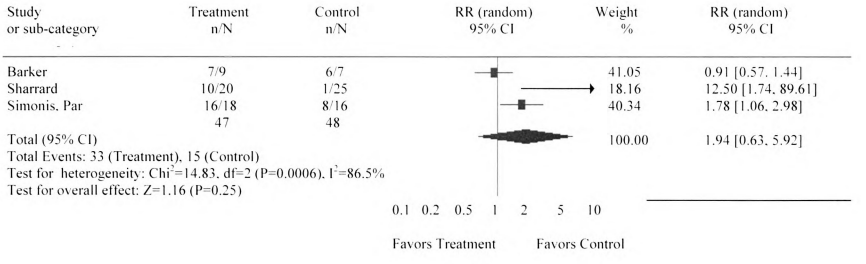


Figure 5 Sensitivity Analysis Drop Sharrard

Review: Efficacy of Electromagnetic Bone Growth Stimulators on Delayed Union and Non Union Fractures
Comparison: 01 Electromagnetic Stimulation vs. Sham Control
Outcome: 04 Sensitivity Analysis (Drop Sharrard)

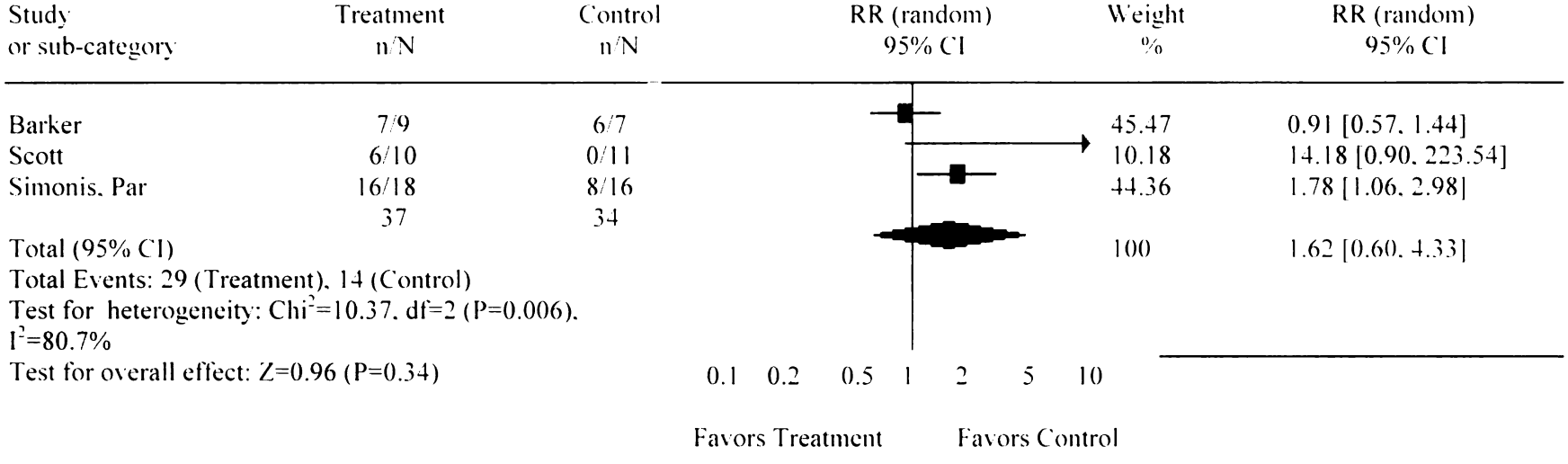
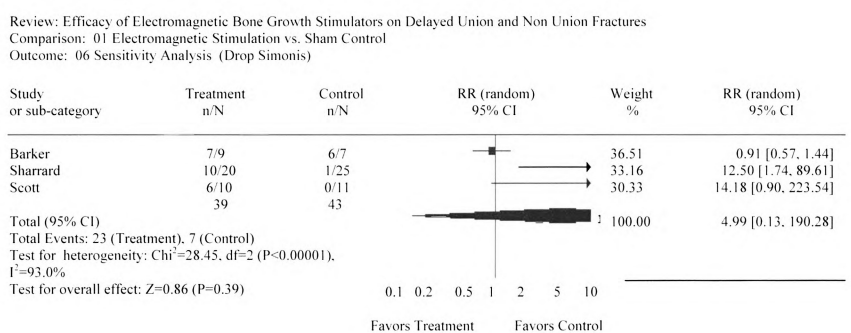


Figure 6 Sensitivity Analysis Drop Simonis



APPENDIX A

Quality Assessments

JADAD QUALITY ASSESSMENT

1) Jadad-If the article has a score less then three, stop here and check not usable at the top.

SCORE:_____

- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Jadad Score Calculation	
Item	**Score**
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/-1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/-1

COCHRANE QUALITY ASSESSMENT

This score will be used for a sensitivity analysis. No studies will be excluded because of this score. **SCORE:_____/ 24**

Items	Scores	Notes
A. Was the assigned treatment adequately concealed prior to allocation?	2 = method did not allow disclosure of assignment 1 = small but possible change of disclosure of assignment unclear 0 = quasi-randomised or open list/tables	Cochrane code (see Handbook) A = clearly yes B = not sure C = clearly no
B. Were the outcomes of patients who withdrew described and included in the analysis (intention to treat)?	2 = withdrawals well described and accounted for in analysis 1 = withdrawals described and analysis not possible 0 = no mention, inadequate mention or obvious differences and no adjustment	
C. Were the outcome assessors blinded to treatment status?	2 = effective action taken to blind 1 = small or moderate chance of unblinding of assessors 0 = mentioned or not possible	
D. Were the treatment and control group comparable at entry?	2 = good comparability of groups or confounding adjusted for in analysis 1 = confounding small; mentioned but not adjusted for 0 = large potential for confounding or not discussed	
E. Were the subjects blind to assignment status after allocation?	2 = effective action taken to blind subjects 1 = small or moderate chance of unblinding of subjects 0 = not possible or not mentioned (unless double-blind) or possible but not	

	done	
F. Were the treatment providers blind to assignment?	2 = effective action taken to blind providers 1 = small or moderate chance of unblinding of providers 0 = not possible or not mentioned (unless double-blind) or possible but not done	
G. Were care programmes other than the trial options identical?	2 = clearly identical 1 = clear but trivial differences 0 = not mentioned or clear and important differences in care programmes	
H. Were the inclusion and exclusion criteria clearly defined?	2 = clearly defined 1 = inadequately defined 0 = not defined	
I. Were interventions clearly defined?	2 = clearly defined 1 = inadequately defined 0 = not defined	
J. Were the outcome measures used clearly defined?	2 = clearly defined 1 = inadequately defined 0 = not defined Outcomes: 1: Clinical consolidation 2: Radiographic consolidation 3: Pain 4: Function 5: Complications due to stimulation	Item score = total score/number of outcomes
K. Were diagnostic tests used in outcome assessment clinically useful?	2 = optimal 1 = adequate 0 = not defined, not adequate Outcomes: 1: Clinical consolidation 2: Radiographic consolidation 3: Pain 4: Function 5: Complications due to stimulation	Item score = total score/number of outcomes
L. Was the duration of surveillance active and clinically appropriate?	2 = optimal 1 = adequate 0 = not defined, not adequate	Item score = total score/number of

	Outcomes: 1: Clinical consolidation 2: Radiographic consolidation 3: Pain 4: Function 5: Complications due to stimulation	outcomes

(Punt et alt., 2004)

APPENDIX B

Meta-Analysis Forms

Relevancy Screening Form Hit number_____

Inclusion Criteria

Injury- *delayed and/or nonunion fractures at any site*

___Delayed union- failure of fracture to unite after three months

___Non union-failure of fracture to unite after six months

Looking for fractures at all sites. This includes all injuries that lead to non-union like past failed surgeries or stress fractures

Does study meet this criteria? (Circle one) Yes No Unsure

Intervention- *bone growth stimulator compared to placebo or sham control only*

___Experimental Group- use one of three types of bone growth stimulators. Direct Current. Capacitive Coupling. or Pulsed Electromagnetic Fields (PEMF)

___Control Group- Bone growth stimulator must be compared to a sham control (fake BGST) or placebo control (no treatment given). Studies that use active control modalities such as ultrasound. or surgery (e.g. bone grafts) are excluded.

Does study meet this criteria? (Circle one) Yes No Unsure

Population- *healthy human population without concomitant disease/conditions*

___Uses healthy humans

___Subjects cannot have any of the following diseases: bone cancer. Insulin Receptor Substrate-1 Deficiency. aplastic anemia. osteoperosis. If nothing is mentioned it will be assumed that the population is healthy.

Does study meet this criteria? (Circle one) Yes No Unsure

Trial Type- *randomized controlled trial or quasi-randomized controlled trial*

___Randomized Controlled Trial- allocate treatment using random numbers table. computer generated allocation. or sealed envelope

___Controlled Clinical Trail (quasi-randomized)- allocate treatment using coin flip. alternative (odd/even number) assignment. patient social security number, days of the week. medical record number. etc.

Does study meet this criteria? (Circle one) Yes No Unsure

Should the article be included in the Meta-Analysis

_____Yes (all the criteria above marked as Yes)

_____ No (at least one criteria marked as No)

_____ Unsure (at least one criteria marked as Unsure)

Data Extraction Form

____ **Useable**
____ **Not Useable: Explain why**_____

ArticleTitle:_____

_____

Analysis Date:_____ Reviewed by:_____

Revman ID:_____

INCLUSION CRITERIA- **If a boxes from each section is not checked/circled, STOP here, check not useable at top, and do not move to Quality Assessment**

1) Type of Trial

☐ *Randomized Controlled Trial*- Studies where the treatments administered are selected by a random process such as the use of a random numbers table, computer generated allocation, random number generator (ERNIE), or a sealed envelope.

☐ *Controlled Clinical Trial*- Treatment allocations using coin flips, odd-even numbers, patient social security numbers, days of the week, medical record numbers, or other such pseudo- or quasi-random processes.

2) Definition of Injury

☐ *Delayed Union*- failure to see normal healing of the bone on radiographic evidence within three to six months of the injury depending on the fracture site.

☐ *Nonunion*- failure to unite beyond six to nine months.

3) Population

☐ Healthy human population, no subjects with diseases that may impede in the bone regeneration process (bone cancer, Insulin Receptor Substrate-1 Deficiency, aplastic anemia, osteoperosis)

Fill in the following information if given

- Age range of population_____
- Mean age _____
- Age specific subgroup results_____ _____

_____

4) Diagnosis of Injury

☐

Radiographic Evidence (x-ray, bone scan, CT scan, MRI)
Type used:_____

☐

5) Interventions (circle one used, if the study does not fit any of the definitions, stop here and check not usable at the top)

- *Uses Direct Current*- uses a generator to deliver electric energy by surgically implanted electrodes into the fusion bed
- *Pulsed electromagnetic fields (PEMF)*- time varying current that travels through metallic coils at a certain duration and intensity, uses electrodes, does not require surgery
- *Capacitive Coupling*- charges two metal plates that are attached to a voltage source and produces electrical field by using electrodes, does not require surgery

☐

6) Control Group/Type of Placebo (circle one used, if the study does not fit any of the definitions, stop here and check not useable at the top)

- *Placebo Control* (control group receives no treatment)
- *Sham Control* (fake BGST, no emit energy/ emits low levels of electricity proven not to stimulate osteogenesis).

7) Outcome

☐

Radiographic Evidence (x-ray, bone scan, CT scan, MRI)
Type used:_____

Time Frame (circle one)

- Finite date to healing set as _____
- Serial measurements taken _____

8) Blinding of Outcome Assessors (check which one applies)

☐

Were the outcome assessors blinded to treatment status
_____ Outcome assessors were blinded (2)
_____ Outcome assessors were not blinded (1)
_____ Blinding of outcome assessors was not mentioned (0)

EXCLUSION CRITERIA- check all that apply, if one or more are checked, stop here and check not usable on top of first page.

___ No type of randomization of the experimental or control group
___ Study uses pain scale, mobility measurement, or return to activity as outcome Assessment

___ Study does not use bone growth stimulators
___ Delayed union defined as failure to heal before three months
___ Nonunion defined as failure to heal before six months
___ Study does not use delayed or nonunion fractures
___ Study uses animals
___ Study uses humans with bone cancer, Insulin Receptor Substrate-1 Deficiency, aplastic anemia, osteoperosis
___ There is no control group in the study
___ Control group treated with ultrasound, hormones, bone grafts, or other types of surgery

QUALITY ASSESSMENT

1) Jadad-If the article has a score less then three, stop here and check not usable at the top.

SCORE:_____

- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Jadad Score Calculation	
Item	**Score**
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/-1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/-1

2) Cochrane Quality assessment tool-This score will be used for a sensitivity analysis. No studies will be excluded because of this score.
SCORE:_____/ 24

Items	Scores	Notes
A. Was the assigned treatment adequately concealed prior to allocation?	2 = method did not allow disclosure of assignment 1 = small but possible change of disclosure of assignment unclear 0 = quasi-randomised or open list/tables	Cochrane code (see Handbook) A = clearly yes B = not sure C = clearly no
B. Were the outcomes of patients who withdrew described and included in the analysis (intention to treat)?	2 = withdrawals well described and accounted for in analysis 1 = withdrawals described and analysis not possible 0 = no mention, inadequate mention or obvious differences and no adjustment	
C. Were the outcome assessors blinded to treatment status?	2 = effective action taken to blind 1 = small or moderate chance of unblinding of assessors 0 = mentioned or not possible	
D. Were the treatment and control group comparable at entry?	2 = good comparability of groups or confounding adjusted for in analysis 1 = confounding small; mentioned but not adjusted for 0 = large potential for confounding or not discussed	
E. Were the subjects blind to assignment status after allocation?	2 = effective action taken to blind subjects 1 = small or moderate chance of unblinding of subjects 0 = not possible or not mentioned (unless double-blind) or possible but not	

	done	
F. Were the treatment providers blind to assignment?	2 = effective action taken to blind providers 1 = small or moderate chance of unblinding of providers 0 = not possible or not mentioned (unless double-blind) or possible but not done	
G. Were care programmes other than the trial options identical?	2 = clearly identical 1 = clear but trivial differences 0 = not mentioned or clear and important differences in care programmes	
H. Were the inclusion and exclusion criteria clearly defined?	2 = clearly defined 1 = inadequately defined 0 = not defined	
I. Were interventions clearly defined?	2 = clearly defined 1 = inadequately defined 0 = not defined	
J. Were the outcome measures used clearly defined?	2 = clearly defined 1 = inadequately defined 0 = not defined Outcomes: 1: Clinical consolidation 2: Radiographic consolidation 3: Pain 4: Function 5: Complications due to stimulation	Item score = total score/number of outcomes
K. Were diagnostic tests used in outcome assessment clinically useful?	2 = optimal 1 = adequate 0 = not defined, not adequate Outcomes: 1: Clinical consolidation 2: Radiographic consolidation 3: Pain 4: Function 5: Complications due to stimulation	Item score = total score/number of outcomes
L. Was the duration of surveillance active and clinically appropriate?	2 = optimal 1 = adequate 0 = not defined, not adequate	Item score = total score/number of outcomes

	Outcomes: 1: Clinical consolidation 2: Radiographic consolidation 3: Pain 4: Function 5: Complications due to stimulation	

(Punt et alt., 2004)

DATA EXTRACTION

1) **Dichotomous Data-** Binary data where each individuals outcome is one of only two possible responses: healed v. not healed

Bone Growth Stimulator		*Control Group*	
Number Healed (n)	Number of Participants (N)	Number Healed (n)	Number of Participants (N)

2) **Continuous Data-** where each individuals outcome is a measure of numerical quantity

Bone Growth Stimulator			*Control Group*		
Number of Participants (N)	Mean	Standard Deviation (SD)	Number of Participants (N)	Mean	Standard Deviation (SD)

REFERENCES

Aaron, R., Ciombor, D., & Simon, B. (2004). Treatment of Nonunions with Electric and Electromagnetic Fields. *Clinical Orthopaedics*, 419, 21-29.

Aetna. (2006). Clinical Policy Bulletin: Bone Growth Stimulators [Announcement posted on the World Wide Web]. American Medical Association. Retrieved September 5, 2007 from the World Wide Web: http://www.aetna.com/cpb/medical/data/300_399/0343.html.

Akai, M., & Hayashi, K. (2002). Effect of Electric Stimulation on Musculoskeletal Systems: A Meta-Analysis of Controlled Clinical Trials. *Bioelectromagnetics*, 23(2), 132-143.

Antonsson, E.K., & Mann, R.W. (1985). The frequency content of gait. *Journal of Biomechanics*, 18, 39-47.

Bassett, C., & Becker, R. (1962). Generation of electric potentials by bone in response to mechanical stress. *Science*, 137, 1063-4.

Bassett, C., Pilla, A., & Pawluk, R. (1977). A non-operative salvage of surgically-resistant pseudarthroses and non-unions by pulsing electromagnetic fields. *Clinical Orthopaedics and Related Research*, 124, 128-143.

Bhandari, M., Richards, R., Sprague, S., & Schemitsch, E. (2001). Letter to the Editor: Quality in the Reporting of Randomized Trials in Surgery: Is the Jadad Scale Reliable? *Controlled Clinical Trials*, 22, 687-688.

Brighton, C.T., Black, J., & Friedenberg, Z.B. (1981). A multicenter study of the treatment of non-union with constant direct current. *Journal of Bone and Joint Surgery*, 63, 2-13.

Bruser, P., & Gilbert, A. (1999). *Finger Bone and Joint Injuries*. London: Martin Dunitz, Ltd.

Clark, H., Wells, G., Huet, C., McAlister, F., et al. (1999). Assessing the Quality of Randomized Trials: Reliability of the Jadad Scale. *Controlled Clinical Trials*, 20, 448-452.

Clark, O., Castro, A., Filho, J., & Djubelgovic, B. (2001). Interrater Agreement of Jadad's Scale. *Proceedings from the 9th International Cochrane Colloquium*, 31. Retrieved November 12, 2007, from BioMed Central.

Caudle, R.J., & Stern, P.J. (1987). Severe open fractures of the tibia. *J Bone Joint Surg Am*,69, 801-807.

Coosemans, W., Rommens, P., Broos, P., & Gruwez, J. (1988). Specific problems in the management of segmental fractures of the tibial shaft [Specifieke behandelingsproblemen bij de bifocale tibiaschaftfractuur]. *Acta Chirurgica Belgica*, 88(5), 347-53.

Diniz, P., Shomura, K., Soejima, K., & Ito, G. (2002). Effects of Pulsed Electromagnetic Field (PEMF) Stimulation on Bone Tissue Like Formation Are Dependent on the Maturation Stages of the Osteoblasts. *Bioelectromagnetics*, 23, 398-405.

Einhorn, T. (1995). Enhancement of fracture-healing. *Journal of Bone & Joint Surgery. American Volume*, **77**(6), 940-56.

Friedenberg, Z., & Brighton, C. (1966). Bioelectric potentials in bone. *Journal of Bone & Joint Surgery. American Volume*, 48(5), 915-23.

Fukada, E., & Yasuda, I. (1957). On the piezoelectric effects of bone. *Nippon seirigaku zasshi. [Journal of the Physiological Society of Japan]*, 12(11), 58-69.

Glasziou, P., Irwig, L., Bain, C., & Colditz, G. (2001). *Systematic Reviews in Health Care. A Practical Guide.* Cambridge: Cambridge University Press.

Hall, B. (1990). *Bone*. Nova Scotia: CRC Press.

Higgins J., & Green S. (2007). *Cochrane Handbook for Systematic Reviews of Interventions 4.2.X*. Retrieved August 13, 2007, from The Cochrane Collaboration Web site: http://www.cochrane.dk/cochrane/handbook/handbook.htm.

Hulme, J., Robinson, V., DeBie, R., Wells, G., Judd, M., & Tugwell, P. (2002). Electromagnetic fields for the treatment of osteoarthritis. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD003523. DOI: 10/1002/14651858.CD003523.

Jadad, A. R., Moore, A., & Carroll, D. (1996). Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Controlled Clinical Trials, 17, 1-12.*

Karamitros, A., Kalentzos, V., & Soucacos, P. (2006). Electric stimulation and hyperbaric oxygen therapy in the treatment of nonunions. *Injury*, 37(1), S63-73.

Khan, K., Kunz, R., Kleijnen, J., & Antes, G. (2003). *Systematic Reviews to Support Evidence-based Medicine. How to Review and Apply Findings of Healthcare Research.* London: The Royal Society of Medicine and Press.

LaVelle, D. (1998). Delayed union and nonunion of fractures. *Campbell's operative orthopaedics*, 9, 2579 -629.

Liboff, AR. (2006). *Encyclopedia of Medical Devices and Instrumentation.* Rochester, MI: John Wiley and Sons, Inc.

Luben, R. (1991). Effects of low-energy electromagnetic fields (pulsed and DC) on membrane signal transduction processes in biological systems. *Health Physics*, 61, 15-28.

Marieb, E. (2001). *Human Anatomy and Physiology.* San Francisco: Benjamin Cummings.

Marsh, D. (1998). Concepts of Fracture union, delayed union, and nonunion. *Clinical Orthopedic Related Resources*, 355, 22-30.

Masami, A., & Hayashi, K. (2002). Effects of Electrical Stimulation on Musculoskeletal Systems; A Meta-Analysis of Controlled Clinical Trials. *Bioelectromagnetics*, 23, 132-143.

McLeod, K.J., & Rubin, C.T. (1990). Frequency specific modulation of bone adaptation by induced electric fields. *Journal of Theoretical Biology*, 145, 385-396.

McLeod, K.J., Rubin, C.T., & Donahue, H.J. (1995). Electromagnetic fields in bone repair and adaptation. *Radio Science*, 30, 233-244.

Moja, P., Telaro, E., D'Amico, R., Moschetti, I., et al. (2005). Assessment of methodological quality of primary studies by systematic reviews: results of the metaquality cross sectional study. *BMJ*, 330, 1053.

Norton, L. (1974). In vivo bone growth in a controlled electric field. *Ann. N.Y. Academy Science*, 238, 466-477.

Oishi, M., & Onesti, S. (2000). Electric Bone Graft Stimulation for Spinal Fusion: A Review. *Neurosurgery*, 47(5), 1041-1056.

Otter, M., McLeod, K., & Rubin, C. (1998). Effects of Electromagnetic Fields in Experimental Fracture Repair. *Clinical Orthopaedics and Related Research*, 355, S90-S104.

Panagiotis, M. (2006). Classification of non-union. *Injury*, 37(9), 927.

Phieffer, L., & Gould, J. (2006). Delayed Unions of the Tibia. *The Journal of Bone and Joint Surgery (American)*, 88, 205-216.

Punt, B., den Hoed, P., & Stijnen, T. (2004). Electromagnetic Field stimulation for the treatment of delayed union or non-union of long bones. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD004960. DOI: 10.1002/14651858.CD004960.

Review Manager (RevMan) [Computer program]. Version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.

Riemer, B.L., DiChristina, D.G., & Cooper, A. (1995). Nonreamed nailing of tibial diaphyseal fractures in blunt polytrauma patients. *J Orthop Trauma*, 9, 66-75.

Ryaby, J. (1998). Clinical Effects of Electromagnetic and Electric Fields on Fracture Healing. *Clinical Orthopaedics and Related Research. Fracture Healing Enhancement*, 335, 205-215.

Saleh, K., & Hak, D. (2001, August). Socioeconomic Burden of Traumatic Tibial Fractures: Nonunion or Delayed Union, *WebMD*, Retrieved September 9, 2007, from Medscape database.

Sanders, R., Jersinovich, I., Anglen, J., DePasquale, T., & Herscovici, D. (1994). The treatment of open tibial shaft fractures using an interlocked intramedullary nail without reaming. *J Orthop Trauma*, 8, 504-510.

Schubert, H. (2000). Scaphoid Fracture Review of Diagnostic Tests and Treatment. *Canadian Family Physician*, 46, 1825-1832.

Sharrard, W. (1990). A double-blind trial of pulsed electromagnetic fields for delayed union on tibial fractures. *Journal of Bone and Joint Surgery*, 72B, 347-355.

Towheed, T. (2006). Is the Jadad Score the Proper Evaluation of Trials? *The Journal of Rheumatology*, 33(8), 1710-1711.

Venes, D., & Thomas, C.L. (1997) *Taber's Cyclopedic Medical Dictionary*. Philadelphia: F.A. Davis Company.

Watson, J. (1979). The Electrical Stimulation of Bone Healing. *Proceedings of the IEEE*, 67(90), 1339-1351.

Younger, E.M., & Chapman, M.W. (1989). Morbidity at bone graft donor sites. J Orthop Trauma, 3, 192.

(2006). *Proposed Reclassification for Bone Growth Stimulator Devices.*

Questions for the Orthopeadic and Rehabilitation Devices Panel. Retrieved October 28, 2007, from The US Food and Drug Administration Website: http://www.fda.gov/default.htm.

REFERENCES TO STUDIES

Included Studies

Barker, A., Dixon, R., Sharrard, W., & Sutcliffe, M. (1984). Pulsed Magnetic Field Therapy for Tibial Non-Union. Interim Results of a Double-Blind Trial. *Lancet*, 8384, 994-6.

Scott, G., & King, J. (1994). A Prospective Double-Blind Trial of Electrical Capacitive coupling in the Treatment of Non-Union of Long Bones. *Journal of Bone and Joint Surgery*, 76(6), 820-6.

Sharrard, W. (1990). A Double-Blind trial of Pulsed Electromagnetic field for Delayed Union of Tibial fractures. *Journal of Bone and Joint Surgery*, 72(3), 374-55.

Simonis, R., Parnell, E., Ray, P., & Peacock, J. (2003). Electrical Treatment of tibial non-union: A Prospective randomized, double-blind trial. *Injury*, 34(5), 357-62.

Excluded Studies

Abdel-Salam, A., Eyres, K., & Cleary, J. (1991). Internal Fixation of closed Tibial fractures for the Management of Sports Injury. *British Journal of Sports Medicine*, 25(4), 213-7.

Adams, C., Robinson, C., Court-Brown, C., & McQueen, M. (2001). Prospective randomized controlled trial of an Intramedullary nail versus Dynamic screw and plate for Intertrochanteric fractures of the Femer. *Journal of Orthopeadic Trauma*, 15(6), 344-400.

Adolfsson, L, Lindau, T., & Arner, M. (2001). Actruak screw fixation versus Cast immobilization for Undisplaced Scaphoid wrist Fractures. *Journal of Hand Surgery*, 26(3), 192-5.

Aldophson, P., Abbazadegan, H., Boden, H., & Salemyr, M. (2000). Clodronate increases Mineralization of Callus after Colles' Fractures: a Randomized, Double-Blind, Placebo-Controlled, Prospective Trial in 32 Patients. *Acta Orthopaedic Scandinavian*, 71(2), 195-200.

Agorastides, I., Sinopidis, C., El Meligy, M., & Yin, Q. (2007). Early versus Late Mobilization after Hemiarthoplasty for Proximal Humeral Fractures. *Journal of Shoulder and Elbow Surgery*, 16(3), S33-8.

Ahl, T., Dalen, N., Lundberg, A., & Wykman, A. (1994). *Acta Orthopaedic Scandanavian*, 65(2), 166-70.

Ahrengart, L., Tornkvist, H., Fornander, P., & Thorngren, K. (2002). A Randomized Study of the Compression Hip Screw and Gamma Nail in 426 Fractures. *Clinical Orthopaedic and Related Research*, 401, 209-22.

Ahuja, S., & Chatterji, S. (2002). The Mennen Femoral Plate for Fixation of Periprosthetic Femoral Fractures following Hip Arthoplasty. *Injury*, 33(1), 47-50.

Akesson, K., Vergnaud, P., Delmas, P., & Obrant, K. (1995). Serum Osteocalcin increases during Fracture Healing in Elderly Women with Hip Fractures. *Bone*, 16(4), 427-30.

Al_Belasy, F. (2005). A Short Period of Maxillomandibular Fixation for the Treatment of Fractures of the Mandibular tooth-bearing area. *Journal of Oral and Maxillofacial Surgery*, 63(7), 1456-8.

Al-Sukhun, J., & Lindqvist, C. (2006). A Comparative Study of Two Implants Used to Repair Inferior Orbital Wall bony Defects: Autogenous Bone Graft versus Bioresorbable Poly-L/DL-Lactide Plate. *Journal of Oral and Maxillofacial Surgery*, 64(7), 1038-48.

Aladin, A., & Davis, T. (2005). Dorsal Fracutre-dislocation of the Proximal Interphalangeal Joint: A Comparative Study of Percutaneous Kirschner Wire Fixation versus Open Reduction and Internal Fixation. *Journal of Hand Surgery*, 30(2), 120-8.

Alho, A., Benterud, J., Ronningen, H., & Hoiseth, A. (1992). Predication of Disturbed Healing in Femoral Neck Fracutre. Radiographic Analysis of 149 Cases. *Acta Orthopaedic Scandanavian*, 63(6), 639-44.

Altay, T., Ozturk, H., Us, R., & Gunal, I. (1999). Four-part Posterior Fracture-Dislocations of the Shoulder. Treatment by Limited Open Reduction and Percutaneous Stabalization. *Acta Orthopaedic Trauma and Surgery*, 199, 1-2.

An, H., Simpson, J., Glover, J., & Stephany, J. (1995) Comparison between Allograft plus Demineralized Bone Matrix versus Autograft in Anterior Cervical Fusion. A Prospective Multicenter Study. *Spine*, 20(20), 2211-6.

Andermahr, J., Elsner, A., Brings, A., & Hensler, T. (2006). Reduced Collagen Degredation in Polytraumas with Traumatic Brain Injury causes Enhanced Osteogenesis. *Journal of Neurotrauma*, 23(5), 708-20.

Antich, A., Androver, P., Marti-Garin, D., Murias-Alvarez, J., & Puente-Alonso, C. (1997). External Fixation and Secondary Nailing of Open Tibial Fractures: A Randomized, Prospective Trial. *Journal of Bone and Joint Surgery*, 79(3), 433-7.

Asazuma, T., Masuoka, K., Motosuneya, T., & Tsuji, T. (2005). Posterior lumbar Interbody Fusion using Dense Hydrozyapatite blocks and Autogenous Iliac Bone: Clinical and Radiographic Examinations. *Journal of Spinal Disorder Technology*, 18, 41-7.

Atkin, D., Bohay, D., Slabaugh, P., & Smith, B. (1995). Treatment of Ulnar Shaft Fractures: a Prospective Randomized Study. *Orthopedics*, 18(6), 543-7.

Atkins, R., Sudhakar, J., & Porteous, A. (1998). Use of modified Ilizarov olive wires as pushing wires. *Journal of Orthopedic Trauma*, 12(6), 436-8.

Audige, L., Griffin, D., Bhandari, M., & Keliam, J. (2005). Path Analysis of factors for Delayed Healing and Nonunion in 416 Operatively Treated Tibial Shaft Fractures. *Clinical Orthopedics and Related Research*, 438, 221-32.

Bach, A., & Hansen, S. (1989). Plates versus External Fixation in Severe Open Tibial Shaft Fractures, A Randomized Trial. *Clinical Orthopedics and Related Research*, 241, 89-94.

Bain, G., Zacrest, A., Paterson, D., & Middleton, J. (1997). Abduction Strength following Intramedullary Nailing of the Femer. *Journal of Orthopedic Trauma*, 11(2), 93-7.

Bansal, R., & Craigen, M. (2007). Fifth Metacarpal Neck Fractures: is follow-up required? *Journal of Hand and Surgery Europe*, 32(1), 69-73.

Bar-On, E., Sagiv, S., & Porat, S. (1998). External fixation or flexible intramedullary nailing for Femoral Shaft Fractures in Children. *Journal of Bone and Joint Surgery*, 80(4), 891-2.

Barquet, A., Francescoli, L., Rienzi, D., & Lopez, L. (2000). Intertrochanteric-subtrochanteric Fractures: Treatment with the long Gamma Nail. *Journal of Orthopedic Trauma*, 14(5), 324-8.

Barrios, C., Brostrom, L., Stark, A., & Walheim, G. (1993). Healing

Complications after Internal Fixation of Trochanteric Hip Fractures: the Prognostic value of Osteoporosis. *Journal of Orthopedic Trauma,* 7(5), 438-42.

Bartonicek, I., & Dousa,, P. (2002). Prospective Randomized Controlled Trial of an Intramedullary nail versus Dynamic screw and plate of Intertrochanteric Fractures of the Femur. *Journal of Orthopedic Trauma,* 16(5), 363-4.

Bast, S., Hoffer, M., & Aval, S. (1998). Nonoperative Treatment for Minimally and Nondisplaced Lateral Condyle Fractures in Children. *Journal of Pediatric Orthopedics,* 18(4), 448-50.

Baumgaertel, F., Dahlen, C., Stiletto, R., & Gotzen, L. (1994). Technique of using the AO-femoral Distractor for Femoral Intramedullary Nailing. *Journal of Orthopedic Trauma,* 8(4), 315-21.

Behrens, F., & Searis, K. (1986). External Fixation of the Tibia. Basic Concepts and Prospective Evaluation. *Journal of Bone and Joint Surgery,* 68(2), 246-54.

Benazzo, F., Mosconi, M., Becarisi, G., & Galli, U. (1995). Use of Capacitive coupled Electric Fields in Stress Fractures in Athletes. *Clinical Orthopedics and Related Research,* 310, 145-9.

Biachut, P., O'Brien, P., Meek, R., & Boekhuyse, H. (1997). Interlocking Intramedullary Nailing with and without Reaming for the Treatment of closed Fractures of the Tibial Shaft: a Prospective, Randomized Study. *Journal of Bone and Joint Surgery,* 79(5), 640-6.

Bibbo, C., & Patel, D. (2006). The Effect of Demineralized Bone Matrix-Calcium Sulfate with Vancomycin on Calcaneal Fractures Healing and Infection Rates: A Prospective Study. *Foot and Ankle International,* 27(7), 487-93.

Billic R., Simic, P., Jelic, M., & Stern-Padovan, R. (2006). Osteogenic protein-1 (BMP-7) accelerates healing of Scaphoid Non-Union with Proximal Pole Sclerosis. *International Orthopedic,* 30(2), 128-34.

Bischoff, R., Buechler, U., De Roche, R., & Jupiter, J. (1994). Clinical Results of Tension Band fixation of Avulsion Fractures of the Hand. *Journal of Hand Surgery,* 19(6), 1019-26.

Blum, J., Janzing, H., Gahr, R., & Langendorff, H. (2001). Clinical Performance of a new medullary humeral nail: Antegrade versus Retrograde Insertion. *Journal of Orthopedic Trauma,* 15(5), 342-9.

Blum, J., Rommens, P., & Janzig, H. (1997). The Unreamed Humeral nail- a Biologial Osteosynthesis of the Upper Arm. *Acta Chir Belg*, 97(4), 184-9.

Bombaci, H., Gereli, A., Kucukyazici, O., & Gorgec, M. (2005). A New Technique of Crossed pins in Supracondylar Elbow Fractures in Children. *Orthopaedics*, 28(12), 1406-9.

Bond, C., Shin, A., McBride, M., & Dao, K. (2001). Percutaneous Screw Fixation or Cast Immobilization for Nondisplaced Scaphoid Fractures. *Journal of Bone and Joint Surgery*, 83(4), 483-8.

Bong, M., Capla, E., Egol, K., & Sorkin, A. (2005). Osteogenic Protien-1 (bone morpohogenic protein-7) Combined with Various Adjuncts in the Treatment of Humeral Diaphyseal Nonunions. *Bull Hosp Jt Dis*, 63(1-2), 20-3.

Boriani, S., De Iure, F., Bettelli, G., & Specchia, L. (1994). The results of a multicenter Italian study on the use of the Gamma nail for the treatment of pertrochanteric and subtrochanteric fractures: a review of 1181 cases. *Chir Organi Mov*,79(2), 193-203.

Borrelli, J., Ricci, W., Anglen, J., Gregush, R., & Engsberg, J. (2006). Muscle strength recovery and its effects on outcome after open reduction and internal fixation of acetabular fractures. *Journal of Orthopedic Trauma*, 20(6), 388-95.

Borsalino, G., Bagnacani, M., Bettati, E., & Fornaciari, F. (1988). Electrical stimulation of human femoral intertrochanteric osteotomies. Double-blind study. *Clinical Orthopaedics and Related Research*, 237, 256-63.

Braakman, M., Oderwald, E., & Haentjens, M. (1998). Functional taping of fractures of the 5th metacarpal results in a quicker recovery. *Injury*, 29(1), 5-9.

Brara, H., & Fessler, R. (2000). The role of anterior lumbar interbody allograft bone dowel fusion as an adjunct to posterior segmental lumbar fixation. *Clinical* Neurosurgery, 47, 528-33.

Braten, M., Helland, P., Grontvedt, T., & Aamondt, A. (2005) External fixation versus locked intramedullary nailing in tibial shaft fractures: a prospective, randomized study of 78 patients. *Archives of Orthopedic Trauma and Surgery* 125(1), 21-6.

Brighton, C., Shaman, P., Heppenstall, R., Esterhai, J., Pollack, S., &

Friedenberg, Z. (1995). Tibial nonunion treated with direct current, capacitive coupling, or bone graft. *Clinical Orthopedic and Related Research*, 321, 223-34.

Brighton, C., Black, J., Friedenberg, Z., Esterhai, J., Day, L., & Connolly, J. (1981). A multicenter study of the treatment of non-union with constant direct current. *Journal of Bone and Joint Surgery*, 63(1), 2-13.

Broos, P., & Reynders, P. (1998). The unreamed AO femoral intramedullary nail, advantages and disadvantages of a new modular interlocking system. A prospective study of 67 cases. *Acta Orthopedic Belgium*, 64(3), 284-90.

Broos, P., & Vanderspeeten, K. (1997). Our first experiences with the Unreamed Femoral Nail (UFN). *Acta Chir Belg*, 97(1), 27-32.

Buciuto, R., & Hammer, R. (2001). RAB-plate versus sliding hip screw for unstable trochanteric hp fractures: stability of the fixation and modes of failure--radiographic analysis of 218 fractures. *Journal of Trauma*, 50(3), 545-50.

Buciuto, R., Hammer, R., & Herder, A. (1997). Spontaneous subcapital femoral neck fracture after healed trochanteric fractures. *Clinical Orthopedic and Related Research*, 342, 156-63.

Buckley, R., Tough, S., McCormack, R., & Pate, G. (2002). Operative compared with nonopertive treatment of displaced intra-articular calcaneal fractures: a prospective, randomized, controlled multicenter trial. *Journal of Bone and Joint Surgery*, 84(10), 1733-44.

Burd, T., Hughes, M., & Anglen, J. (2003). Heterotopic ossification prophylaxis with indomethacin increases the risk of long-bone nonunion. *Journal of Bone and Joint Surgery*, 85(7), 700-5.

Cakirgil, G., Saplakoglu, A., & Yazar, T. (1989).The compared effect of a four-coiled system in pulsed electromagnetic field stimulation. *Orthopedics*, 12(11), 1481-4.

Calhoun, J., Henry, S., Anger, D., & Cobos, J. (1993). The treatment of infected nonunions with gentamicin-polymethylmethacrylate antibiotic beads. *Clinical Orthopedics and Related Research*, 295, 23-7.

Canadian Orthopaedic Trauma Society. (2003). Nonunion following intramedullary nailing of the femur with and without reaming. Results of a multicenter randomized clinical trial. *Journal of Bone and Joint Surgery*, 85(11), 2093-6.

(2007). Nonoperative treatment compared with plate fixation of displaced midshaft clavicular fractures. A multicenter, randomized clinical trial. *Journal of Bone and Joint Surgery*, 89(8), 1866-7.

Capanna, R., Donati, D., Masetti, C., & Manfrini, M. (1994). Effect of electromagnetic fields on patients undergoing massive bone graft following bone tumor resection. A double blind study. *Clinical Orthopedics and Related Research*, 306, 213-21.

Carragee, E. (1997). Single-level posteriolateral arthrodesis, with or without posterior decompression, for the treatment of isthmic spondylolisthesis in adults. A prospective, randomized study. *Journal of Bone and Joint Surgery*, 79(8), 1175-80.

Caruso, G., Lagalla, R., Derchi, L., & Iovane, A. (2000). Monitoring of fracture calluses with color Doppler sonography. *Journal of Clinical Ultrasound*, 28(1), 20-7.

Cassinelli, E., Young, B., Vogt, M., & Pierce, M. (2005). Spica cast application in the emergency room for select pediatric femur fractures. *Journal of Orthopedic Trauma*, 19(10), 709-16.

Castillo, R., Bosse, M., MacKenzie, E., & Patterson, B. (2005). Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures. *Journal of Orthopedic Trauma*, 19(3), 151-7.

Ceffa, R., Bombelli, M., Boero, S., & Marre Brnenghi, G. (1997). Extensimetric monitoring of healing in the treatment with the Ilizarov apparatus. A multicenter clinical trial. *Bull Hospital and Joint Disease*, 56(1), 41-5.

Chan, Y., Ueng, S., Wang, C., & Lee, S. (2000). Antibiotic-impregnated autogenic cancellous bone grafting is an effective and safe method for the management of small infected tibial defects: a comparison study. *Journal of Trauma*, 48(2), 245-55.

Chapman, J., Henley, M., Agel, J., & Benca, P. (2000). Randomized prospective study of humeral shaft fractures fixation: intramedullary nails versus plates. *Journal of Orthopedic Trauma*, 14(3), 162-6.

Chapman, M., Bucholz, R., & Cornell, C. (1997). Treatment of acute fractures with a collagen-calcium phosphate graft material. A randomized clinical trial. *Journal of Bone and Joint Surgery*, 79(4), 495-502.

Charalambous, C., Siddique, I., Zenios, M., & Roberts, S. (2005). Early versus

delayed surgical treatment of open tibial fractures: effect on the rates of infection and need of secondary surgical procedures to promote bone union. *Injury*, 36(5), 656-61.

Chen, C., Chen, W., & Shih, C. (2002). Surgical treatment for distal clavicle fracture with coracoclavicular ligament disruption. *Journal of Trauma*, 52(1), 72-8.

Chen, A., Hou, J., Bao, J., & Guo, S. (1998). Comparison of biodegradeble and metallic tension-band fixation for patella fractures. 38 patients followed for 2 years. *Acta Orthopedic Scandanavia*, 69(1), 39-42.

Chevalley, F., & Gamba, D. (1997). Gamma nailing of pertrochanteric and subtrochanteric fractures: clinical results of a series of 63 consecutive cases. *Journal of Orthopedic Trauma*, 11(6), 412-5.

Chiu, F., Chen, C., Lin, C., & Lo, W. (1997). Closed humeral shaft fractures: a prospective evaluation of surgical treatment. *Journal of Trauma*, 43(6), 947-51.

Chiu, F., Lo, W., Chen, C., & Chen, T. (1996). Unstable closed tibial shaft fractures: a prospective evaluation of surgical treatment. *Journal of Trauma*, 40(6), 987-91.

Chu, F., Lo, W., Chen, C., & Chen, T. (1996). Treatment of unstable tibial fractures with interlocking nail versus Ender nail: a prospective evaluation. *Zhonghua Yi Xue Za Zhi*, 57(2), 124-33.

Cho, T., Chol, I., Chung, C., & Yoo, W. (2006). Isolated congenital pseudarthrosis of the fibula: clinical course and optimal treatment. *Journal of Pediatric Orthopedics*, 26(4), 449-54.

Choi, B., Kim, H., Kim, M., & Han, S. (2005). Management of mandibular angle fractures using the mandibular angle reduction forceps. *International Journal of Oral and Maxillofacial Surgery*, 34(3), 257-61.

Choi, B., Huh, J., & Yoo, J. (2003). Computed tomographic findings of the fractured mandibular condyle after open reduction. *International Journal of Oral and Maxillofacial Surgery*, 32(5), 469-73.

Christie, J., Howie, C., & Armour, P. (1988). Fixation of displaced subcapital femoral fractures. Compression screw fixation versus double divergent pins. *Journal of Bone and Joint Surgery*, 70(2), 199-201.

Clatworthy, M., Clark, D., Gray, D., & Hardy, A. (1998). Reamed versus

unreamed femoral nails. A randomized, prospective trial. *Journal of Bone and Joint Surgery*, 80(3), 485-9.

Clinkscales, C., & Peterson, H. (1997). Isolated closed diaphyseal fractures of the femur in children: comparison of effectiveness and cost of several treatment methods. *Orthopedics*, 20(12), 1131-6.

Cohen, A., & Shaw, D. (2001). Focused rigidity casting: a prospective randomised study. *J R Coll Surg Edinb*, 46(5), 265-70.

Cole, R., Bindra, R., Evanoff, B., & Gilula, L. (1997). Radiographic evaluation of osseous displacement following intra-articular fractures of the distal radius: reliability of plain radiographys versus computed tomography. *Journal of Hand Surgery*, 22(5), 792-800.

Collinge, C., Devinney, S., Herscovici, D., & DiPasquale, T. (2006). Anterior-inferior plate fixation of middle-third fractures and nonunions of the clavicle. *Journal of Orthopedic Trauma*, 20(10), 680-6.

Colterjohn, N., & Bednar, D. (1997). Procurement of bone graft from the iliac crest. An operative approach with decreased morbidity. *Journal of Bone and Joint Surgery*, 79(5), 756-9.

Coupland, R., Hoikka, V., Sjoeklint, O., & Cuenod, P. (1992). Assessment of bullet disruption in armed conflicts. *Lancet*, 339(8784), 35-7.

Court-Brown, C., Walker, C., Garg, A., & McQueen, M. (1999). Half-ring external fixation in the management of tibial plafond fractures. *Journal of Orthopedic Trauma*, 13(3), 200-6.

Crutchfield, E., Seligson, D., Henry, S., & Warnholtz, A. (1995). Tibial pilon fractures: a comparative clinical study of management techniques and results. *Orthopedics*, 18(7), 613-7.

Cundy, P., & Paterson, D. (1990). A ten-year review of treatment of delayed union and nonunion with an implanted bone growth stimulator. *Clinical Orthopedic and Related Research*, 259,216-22.

Dazinger, M., Caucci, D., Zecher, S., & Segal, D. (1995). Treatment of intercondylar and supracondylar distal femur fractures using the GSH supracondylar nail. *American Journal of Orthopedics*, 24(9), 684-90.

De Ridder, V., de Lange, S., Koomen, A., & Heatley, F. (2001). Partridge osteosynthesis: a prospective clinical study on the use of nylon cerclage bands in the treatment of periprosthetic femoral shaft fractures. *Journal of Orthopedic Trauma*, 15(1), 61-5.

Deshmukh, R., Lou, K., Neo, C., & Yew, K. (1998). A technique to obtain correct rotational alignment during closed locked intramedullary nailing of the femur. *Injury*, 29(3), 207-10.

Dhakai, A., & Awais, S. (2003). Management of femur shaft fracture with close locked intramedullary nailing: comparison of Variwall and predrilled Kuntscher nail. *Nepal Med Coll Journal*, 5(2), 73-8.

Dias, J., Wildin, C., Bhowal, B., & Thompson, J. (2005). Should acute scaphoid fractures be fixed? A randomized controlled trial. *Journal of Bone and Joint Surgery*, 87(10), 2160-8.

Dickson, K., Friedman, J., Buchholz, J., & Flandry, F. (2002). The use of BoneSource hydroxyapatite cement for traumatic metaphyseal bone void filling. *Journal of Trauma*, 53(6), 1103-8.

Doetsch, A., Faber, J., Lynnerup, N., & Watjen, I. (2004). The effect of calcuim and vitamin D3 supplementation on the healing of the proximal humerus fracture: a randomized placebo-controlled study. *Calcification Tissue International*, 75(3), 183-8.

Doi, K., & Sakai, K. (1994). Vascularized periosteal bone graft from the supracondylar region of the femur. *Microsurgery*, 15(5), 305-15.

Domb, B., Sponseller, P., Ain, M., & Miller, N. (2002). Comparison of dynamic versus static external fixation for pediatric femur fractures. *Journal of Pediatric Orthopedic*, 22(4), 428-30.

Donati, D., Capanna, R., Campanacci, D., & Del Ben, M. (1993). The use of massive bone allografts for intercalary reconstruction and arthrodeses after tumor resection. A multicentric European study. *Chir Organi Mov*, 78(2), 81-94.

Dujardin, F., Benez, C., Polle, G., & Alain, J. (2001). Prospective randomized comparison between a dynamic hip screw and a mini-invasive static nail in fractures of the trochanteric area: preliminary results. *Journal of Orthopedic Trauma*, 15(6), 401-6.

Durmus, A., Cakmak, A., Disci, R., & Muslumanoglu, L. (2004). The efficiency of electromagnetic field treatment in Complex Regional Pain Syndrome Type I. *Disability and Rehabilitation*, 26(9), 537-45.

Earnshaw, S., Aladin, A., Surendran, S., & Moran, C. (2002). Closed reduction of

colles fractures: comparison of manual manipulation and finger-trap traction: a prospective, randomized study. *Journal of Bone and Joint Surgery*, 84(3), 354-8.

Ebinger, T., Roesch, M., Wachter, N., & Kinzl, L. (2001). Functional treatment of physeal and periphyseal injuries of the metacarpal and proximal phalangeal bones. *Journal of Pediatric Surgery*, 36(4), 611-5.

Egol, K., Su, E., Tejwani, N., & Sims, S. (2004). Treatment of complex tibial plateau fractures using the less invasive stabilization system plate: clinical experience and a laboratory comparison with double plating. *Journal of Trauma*, 57(2), 340-6.

Egol, K., Dolan, R., & Koval, K. (2000). Functional outcome of surgery for fractures of the ankle. A prospective, randomized comparison of management in a cast or a functional brace. *Journal of Bone and Joint Surgery*, 82(2), 246-9.

Ekelund, L., Hagberg, L., Horberg, L., & Jorgsholm, P. (2007). Imaging of four-corner fusion (SLAC arthrodesis) of the wrist with 64-slice computed tomography. *Acta Radiol*, 48(1), 76-9.

El-Mowafi, H., Abulsaad, M., & El-Adi, W. (2005). Prophylactic surgical correction of Crawford's type II anterolateral bowing of the tibia using Ilizarov's method. *Acta Orthop Belg*, 71(5), 577-81.

El-Said, N. (1999). Osteotomy of the tibia for correction of complex deformity. *Journal of Bone and Joint Surgery*, 81(5), 780-2.

Emami, A., Larsson, A., Petren-Mallmin, M., & Larsson, S. (1999). Serum bone markers after intramedullary fixed tibial fractures. *Clinical Orthopedic and Related Research*, 368, 220-9.

Epstein, N. (2002). Anterior dynamic plates in complex cervical reconstructive surgeries. *Journal of Spinal Disorder Techniques*, 15(3), 221-7.

Epstein, N. (2000). Anterior cervical diskectomy and fusion without plate instrumentation in 178 patients. *Journal of Spinal Disorders*, 13(1), 1-8.

Etchebehere, E., Caron, M., Pereira, J., & Lima, M. (2001). Activation of the growth plates on three-phase bone scintigraphy: the explanation for the overgrowth of fractures femurs. *European Journal of Nuclear Medicine*, 28(1), 72-80.

Eyres, K., Saleh, M., & Kanis, J. (1996). Effect of pulsed electromagnetic fields

on bone formation and bone loss during limb lengthening. *Bone*, 18(6), 505-9.

Eyres, K., Saleh, M., & Kanis, J. (2004). Effect of pulsed electromagnetic fields on bone formation and bone loss during limb lengthening: a preliminary report. *Journal of Bone and Joint Surgery*, 76, 92.

Faria, M., Lu, Y., Heaney, K., & Uthamanthil, R. (2007). Recombinant human bone morphogenetic protien-2 in absorbable collagen sponge enhances bone healing of tibial osteotomies in dogs. *Veterinarian Surgery*, 36(2), 122-31.

Ferguson, J., & Nicol, R. (2000). Early spica treatgment of pediatric femoral shaft fractures. *Journal of Pediatric Orthopedics*, 20(2), 189-92.

Fernandez, A., & Masliah Galante, R. (2001). Osteosynthesis of diaphyseal fractures of the radius and ulna using an internal fixator (PC-Fix). A prospective study. *Injury*, 32(2), 44-50.

Fernandez Fairen, M., Guillen, J., Busto, J., & Roura, J. (1999). Fractures of the fifth metatarsal in basketball players. *Knee Surgery, Sports Traumatology and Arthroscopy*, 7(6), 373-7.

Finkemeier, C., Schmidt, A., Kyle, R., & Templeman, D. (2000). A prospective, randomized study of intramedullary nails inserted with and without reaming for the treatment of open and closed fractures of the tibial shaft. *Journal of Orthopedic Trauma*, 14(3), 187-93.

Fischer, G., Pelka, R., & Barovic, J.(2005). Adjuvant treatment of knee osteoarthritis with weak pulsing magnetic fields. Results of a placebo-controlled trial prospective clinical trial. *Orthopedie und ihre Grenzgebiete*, 145(5), 544-50.

Fleming, B., Krag, M., Huston, D., & Sugihara, S. (2000). Pin loosening in a halo-vest orthosis: a biomechanical study. *Spine*, 25(11), 1325-31.

Flinkkila, T., Nikkola-Sihto, A., Raatikainen, T., & Junila, J. (1999). Role of metaphyseal cancellous bone defect size in secondary displacement in Colles' fracture. *Archives of Orthopedic and Trauma Surgery*, 119(5-6), 319-23.

Foead, A., Penafort, R., Saw, A., & Sengupta, S. (2004). Comparison of two methods of percutaneous pin fixation in displaced supracondylar fractures of the humerus in children. *Journal of Orthopedic Surgery*, 12(1), 76-82.

Fourie, J., & Thompson, M. (1998). A model for the prediction of time to union in

fracutres of the tibia. *Physiotherapy Research International*, 3(1), 27-36.

Fourie, J., & Bowerbank, P. (1997). Stimulation of bone healing in new fractures of the tibial shaft using interferential currents. *Physiotherapy Research International*, 2(4), 255-68.

Franck, W., Ollvieri, M., Jannasch, O., & Hennig, F. (2003). Expandable nail system for osteoporotic humeral shaft fractures: preliminary results. *Journal of Trauma*, 54(6), 1152-8.

Friedlaender, G. (2004). Osteogenic protein-1 in treatment of tibial nonunions: current status. *Surgical Technology International*, 13, 249-52.

Friedlaender, G., Perry, C., Cole, J., & Cook, S. (2001). Osteogenic protein-1 (bone morphogenetic protein-7) in the treamtne of tibial nonunions. *Journal of Bone and Joint Surgery*, 83, 151-8.

Fritz, T., Weiss, C., Kriegistein, C., & Quentmeier, A. (1999). The classic nail in the therapy of trochanteric fractures. A prospective, controlled study. *Archive of Orthopedic and Trauma Surgery*, 199(5-6), 308-14.

Fritz, T., Hiersemann, K., Kriegistein, C., & Friedl, W. (1999). Prospective randomized comparison of gliding nail and gamma naili in the therapy of trochanteric fractures. *Archives of Orthopedic and Trauma Surgery*, 199(1-2), 1-6.

Furian, J., Perrin, R., Govender, P., & Petrenko, Y. (2007). Use of osteogenic protien-1 in patients at high risk for spinal pseudarthrosis: a prospective cohort study assessing safety, health-related quality of life, and radiograph fusion. *Neurosurgical Spine*, 7(5), 486-495.

Gaebler, C., Berger, U., Schandelmaier, P., & Greitbauer, M. (2001). Rates and odds ratios for complications in closed and open tibial fractures treated with unreamed, small diameter tibial nails: a multicenter analysis of 467 cases. *Journal of Orthopedic Trauma*, 15(6) 415-23.

Gaetani, P., Almar, E., Panella, L., & Levi, D. (2006). Functional disability after instrumented stabalization in lumbar degenerative spondylolisthesis: a follow-up study. *Functional Neurology*, 21(1), 31-7.

Galatz, L., Williams, G., Fenlin, J., & Ramsey, M. (2004). Outcome of open reduction and internal fixation of surgical neck nonunions of the humerous. *Journal of Orthopedic Trauma*, 18(2), 63-7.

Gerlach, K., & Schwarz, A. (2002). Bite forces in patients after treatment of

mandibular angle fractures with miniplate osteosynthesis according to Champy. *International Journal of Oral Maxillofacial Surgery*, 31(4), 345-8.

Gicquel, P., Giacomelli, M., Karger, C., & Calvert, J. (2005). Treatment of epiphyseo-metaphyseal fractures in children with an orginal implant. The threaded pin with an adjustable lock (Fixano). *Operational Orthopedic Traumatology*, 17(1), 51-65.

Ginandes, C., & Rosenthal, D. (1999). Using Hypnosis to accelerate the healing of bone fractures: a randomized controlled pilot study. *Alternative Therapy Health and Medicine*, 5(2), 67-75.

Giordano, N., Battisti, E., Geraci, S., & Fortunato, M. (2001). Effect of electromagnetic fields on bone mineral density and biomechanial markers of bone turnover in osteoporosis: A single-blind, randomized pilot study. *Current Therapeutic Research*, 62(3), 187-193.

Gogus, A., Ozturk, C., Tezer, M., & Camurdan, K. (2007). "Sandwich technique" in the surgical treatment of primary complex fractures of the femur and humerus. *International Orthopedics*, 31(1), 87-92.

Goldhagen, P., O'Conner, D., Schwarze, D., & Schwartz, E. (1994). A prospective comparative study of the compression hip screw and the gamma nail. *Journal of Orthopedic Trauma*, 8(5), 367-72.

Gomar, F., Orozco, R., Villar, J., & Arrizabalaga, F. (2007). P-15 small peptide bone graft substitute in the treatment of non-unions and delayed union. A pilot clinical trial. *International Orthopedics*, 31(1), 93-9.

Goodwin, C., Brighton, C., Guyer, R., & Johnson, J. (1999). A double-blind study of capacitively coupled electrical stimulation as an adjunct to lumbar spinal fusions. *Spine*, 24(13), 1349-56.

Gopal, S., & Giannoudis, P. (2001). Prospective randomized study of reamed versus unreamed femoral intramedullary nailing: an assessment of procedures. *Journal of Orthopedic Trauma*, 15(6), 458-60.

Govender, S., Csimma, C., Genant, H., & Valentin-Opran, A. (2002). Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *Journal of Bone and Joint Surgery*, 84(12), 2123-34.

Graham, J. (1968). Early of delayed weight-bearing after internal fixation of

transcervical fracture of the femur. A clinical trial. *Journal of Bone and Joint Surgery*, 50(3), 562-9.

Gregory, P., Sullivan, J., & Herndon, W. (1995). Adolescent femoral shaft fractures: ridged versus flexible nails. *Orthopedics*, 18(7), 645-7.

Grill, F., Bollini, G., Dungl, P., & Fixsen, J. (2000). Treatment approaches for congenital pseudarthrosis of tibia: results of the EPOS multicenter study. European Paediatric Orthopaedic Society (EPOS). *Journal of Pediatric Orthopedics*, 9(2), 75-89.

Grose, A., Gardner, M., Hettrich, C., & Fishman, F. (2007). Open reduction and internal fixation of tibial pilon fractures using a lateral approach. *Journal of Orthopedic Trauma*, 21(8), 530-7.SO:J Orthop Trauma

Grubb, S., Lipscomb, H., & Suh, P. (1994). Results of surgical treatment of painful adult scoliosis. *Spine*, 19(14), 1619-27.

Gruen, T., Poggie, R., Lewallen, D., & Hanssen, A. (2005). Radiographic evaluation of a monoblock acetabular component: a multicenter study with 2- to 5-year results. *Journal of Arthroplasty*, 20(3), 369-78.

Gunal, I., Ozcelik, A., Gokturk, E., Ada, S., & Demirtas, M. (1999). Correlation of magnetic resonance imaging and intraoperative punctate bleeding to assess the vascularity of scaphoid nonunion. *Archives of Orthopedic and Trauma Surgery*, 119(5-6), 285-7.

Gupta, R., Raheja, A., & Modi, U. (1999). Colles' fracture: management by percutaneous crossed-pin fixation versus plater of Paris cast immobilization. *Orthopedics*, 22(7), 680-2.

Gustilo, R., Gruninger, R., & Davis, T. (1987). Classification of type III (severe) open fractures relative to treatment and results. *Orthopedics*, 10(12), 1781-8.

Haas, N., Hauke, C., Schutz, M., & Kaab M. (2001). Treatment of diaphyseal fractures of the forearm using the Point Contact Fixator (PC-Fix): results of 387 fractures of a prospective multicentric study (PC-Fix II). *Injury*, 32, 851-62.

Haidukewych, G., Sems, S., Huebner, D., Horowitz, D., & Levy, B. (2007). Results of polyaxial locked-plate fixation of periarticular fractures of the knee. *Journal of Bone and Joint Surgery*, 89(3), 614-20.

Haidukewych, G., & Berry, D. (2003). Salvage of failed internal fixation of

intertrochanteric hip fractures. *Clinical Orthopedic and Related Research*, 412, 184-8.

Hammacher, E., van Meeteren, M., & van der Werken, C. (1998). Improved results in treatment of femoral shaft fractures with the unreamed femoral nail? A multicenter experience. *Journal of Trauma*, 45(3), 517-21.

Handolin, L., Kitjunen, V., Arnaia, I., & Kiuru, M. (2005) No long-term effects of ultrasound therapy on bioabsorbable screw-fixed lateral malleolar fracture. *Scandanavian Journal of Surgery*, 94(3), 239-42.

Handolin, L., Kiljunen, V., Arnala, I., & Kiuri M. (2005). Effect of ultrasound therapy on bone healing of lateral malleolar fractures of the akel joint fixed with bioabsorbable screws. *Journal of Orthopedic Science*, 10(4), 391-5.

Handolin, L., Kiljunen, V., Arnala, I., & Pajarinen, J. (2005). The effect of low intensity ultrasound and bioabsorbable self-reinforced poly-L-lactide screw fixation on bone in lateral malleolar fractures. *Archives of Orthopedic and Trauma Surgery*, 125(5), 317-21.

Hanft, J., Goggin, J., Landsman, A., & Suprenant, M. (1998). The role of cobined magnetic field bone growth stimulation as an adjunct in the treatment of neuroarthropathy/Charcot joint: an expanded pilot study. *The Journal of Foot and Ankle Surgery*, 37(6), 510-5.

Hansen, P., & Hansen, T. (1998). The treatment of fractures of the ring and little metacarpal necks. A prospective randomized study of three different types of treatment. *Journal of Hand Surgery*, 23(2), 245-7.

Harding, I., Parry, D., & Barrington, R. (2001). The use of a molded metacarpal brace versus neighbor strapping for fracture of the little finger metacarpal neck. *Journal of Hand Surgery*, 26(3), 261-3.

Hardy, D., Descamps, P., Krallis, P., & Fabeck, L. (1998). Use of an intramedullary hip-screw compared with a compression hip-screw with a plate for intertrochanteric femoral fractures. A prospective, randomized study of one hundred patients. *Journal of Bone and Joint Surgery*, 80(5), 618-30.

Harrison, W., Lewis, C., & Lavy, C. (2004). Open fractures of the tibia in HIV positive patients: a prospective controlled single-blind study. *Injury*, 35(9), 852-6.

Heck, B., Ebraheim, N., & Foetisch, C. (1997). Direct complication of

trochanteric osteotomy in open reduction and internal fixation of acetabular fractures. *American Journal of Orthopedics*, 26(2), 124-8.

Heetveld, M., Raaymakers, E., van Eck-Smit, B., & van Walsum, A. (2005). Internal fixation for displaced fractures of the femaoral neck. Does bone density affect clinical outcome? *Journal of Bone and Joint Surgery*, 87(3), 367-73.

Helfet, D., Howey, T., Dipasquale, T., & Sanders, R. (1994). The treatment of open and or unstable tibial fractures with an unreamed double-locked tibial nail. *Orthopedic Review*, Supp, 9-17.

Henie, P., Zimmermann, G., & Weiss, S. (2005). Matrix metalloproteinases and failed fracture healing. *Bone*, 37(6), 791-8.

Henley, M., Chapman, J., Agel, J., & Harvey, E. (1998). Treatment of type II, IIIA, and IIIB open fractures of the tibial shaft: a prospective comparison of unreamed interlocking intramedullary nails and half-pin external fixators. *Journal of Orthopedic Trauma*, 12(1), 1-7.

Hernefalk, L., Granstrom, P., & Messner, K. (1997). Sequential scintigraphy and orthoradiographic measurement of femoral shortening after femoral neck fractures. *Archives of Orthopedic and Trauma Surgery*, 116(4), 198-203.

Hernefalk, L., & Messner, K. (1996). Rigid osteosynthesis decreases the late complication rate after femoral neck fracture. The influence of three different osteosynthesis devices evaluated in 369 patients. *Archives of Orthopedic and Trauma Surgery*, 115(2), 71-4.

Herscovici, D., Ricci, W., McAndrews, P., DiPasquale, T., & Sanders, R. (2000). Treatment of femoral shaft fractures using unreamed interlocked nails. *Journal of Orthopedic Trauma*, 14(1), 10-14.

Hertel, R., Eljer, H., Meisser, A., & Hauke, C. (2001).Biomechanical and biological considerations relating to the clinical use of the Point Contact-Fixator--evaluation of the device handling test in the treatment of diaphyseal fractures of the radius and/or ulna. *Injury*, 32, 10-14.

Hertel, R., Lambert, S., Muller, S., Ballmer, F., & Ganz, R. (1999). On the timing of soft-tissue reconstruction for open fractures of the lower leg. *Archives of Orthopedic and Trauma Surgery*, 199(1-2), 7-12.

Hinsenkamp, M., Ryaby, J., & Burny, F. (1985). Treatment of Non-Union by Pulsing Electromagnetic Field: European Multicenter Study of 308 Cases. *Reconstruction Surgery Traumatology*, 19, 147-151.

Hofmann, G., Conschorek, O., & Buhren, V. (1999). Segment transport employing intramedullary devices in tibial bone defects following trauma and infection. *Journal of Orthopedic Trauma*, 13(3), 170-7.

Hull, J., Sanderson, P., Rickman, M., & Bell, M. (1997). External fixation of children's fractures: use of the Orthofix Dynamic Axial Fixator. *Journal of Pediatric Orthopedics* 6(3), 203-6.

Huusko, T., Karppi, P., Kautiainen, H., & Suominen, H. (2002). Randomized, double-blind, clinically controlled trial of intranasal calcitonin treatment in patients with hip fracture. *Calcif Tissue International*, 71(6), 478-84.

Iannacone, W., Bennett, F., Delong, W., & Born, C. (1994). Initial experience with the treatment of supracondylar femoral fractures using the supracondylar intramedullary nail: a preliminary report. *Journal of Orthopedic Trauma*, 8(4), 322-7.

Iida, Y., Kuroda, T., Kitano, T., & Mizuno, K. (2000). Dexa-measured bone density changes over time after intertrochanteric hip fractures. *Kobe Journal of Medical Science*, 46(1-2), 1-12.

Inan, M., El Rassi, G., Riddle, E., & Kumar, S. (2006). Residual deformities following successful initial bone union in congenital pseudoarthrosis of the tibia. *Journal of Pediatric Orthopedics*, 26(3), 393-9.

Ingman, A. (2000). Percutaneous intramedullary fixation of trochanteric fractures of the femur. Clinical trial of a new hip nail. *Injury*, 31(7), 483-7.

Iseda, T., Nakano, S., Suzuki, Y., & Miyahara, D. (2000). Radiographic and scintigraphic courses of union in cervical interbody fusion: hydroxyapatite grafts versus iliac bone autografts. *Journal of Nuclear Medicine*, 41(10), 1642-5.

Isiklar, Z., Demirors, H., Akpinar, S., & Tandogan, R. (1999). Two-stage treatment of chronic staphylococcal orthopaedic implat-related infections using vancomycin impregnated PMMA spacer and rifampin containing antibiotic protocol. *Bull Hosp Joint Disease*, 58(2), 79-85.

Jacobson, J., Gorman, R., Yamanashi, W., Saxena, B., & Clayton, L. (2001). Low-amplitude, extremely low frequency magnetic fields for the treatment of osteoarthritic knees: a double-blind clinical study. *Alternative Therapies in Health and Medicine*, 7(5), 54-64.

Jamdar, J., Rao, B., Netke, S., & Roomi, M. (2004). Reduction in tibial shaft

fracture healing time with essential nutrient supplementation containing ascorbic acid, lysine, and praline. *Journal of Alternative Complement Medicine*, 10(6), 915-6.

Jazrawi, L., Kummer, F., Simon, J., & Bai, B. (2000). New technique for treatment of unstable distal femur fractures by locked double-plating: case report and biomechanical evaluation. *Journal of Trauma*, 48(1), 87-92. SO:J Trauma

Jenis, L., An, H., Stein, R., & Young, B. (2000). Prospective comparison of direct current electrical stimulation and pulsed electromagnetic fields on instrumented posterolateral lumbar arthrodesis. *Journal of Spinal Disorders*, 13(4), 290-6.

Jenis, L., An, H., Stein, R., & Young, B. (2000). Prospective comparison of the effect of direct current electrical stimulation and pulsed electromagnetic fields on instrumented posterolateral lumbar arthrodesis. *Journal of Spinal Disorders*, 13(4), 290-6.

Jensen, C., & Jensen, C. (1996). Biodegradable pins versus Kirschner wires in hand surgery. *Journal of Hand Surgery*, 21(4), 507-10.

Jeyam, M., Andrew, J., Muir, L., & Mcgovern, A. (2002). Controlled trial of distal radial fractures treated with a resorbable bone mineral substitute. *Journal of Hand Surgery*, 27(2), 146-9.

Johnson, L., Morrison, K., & Wood, D. (2000). The application of arthroscopic principles to bone grafting of delayed union of long bone fractures. *Arthroscopy*, 16(3), 279-89.

Jones, A. (2005). Recombinant human bone morphogenic protein-2 in fracture care. *Journal of Orthopedic Trauma*, 19(10), S23-5.

Joseph, B., & Mathew, G. (2000). Management of congenital pseudarthrosis of the tibia by excision of the pseudarthrosis, only grafting, and intramedullary nailing. *Journal of Pediatric Orthopedics*, 9(1), 16-23.

Jupiter. (1997). Repair of five distal radius fractures with an investigational cancellous bone cement: a preliminary report. *Journal of Orthopedic Trauma*, 11(2), 110-6.

Kabak, S., Halici, M., Tuncel, M., & Avsarogullari, L. (2004). Treatment of midclavicular nonunion: comparison of dynamic compression plating and low-contact dynamic compression plating techniques. *Journal of Shoulder and Elbow Surgery*, 13(4), 396-403.

Kaewpornsawan, K. (2001). Comparison between closed reduction with percutaneous pinning and open reduction with pinning in children with closed totally displaced supracondylar humeral fractures: a randomized controlled trial. *Journal of Pediatric Orthopedics*, 10(2), 131-7.

Kanai, H., Igarashi, M., Yamamoto, S., & Oda, H. (1999). Spontaneous subcapital femoral neck fracture complicating a healed intertrochanteric fracture. *Archives of Orthopedic and Trauma Surgery*, 119(5-6), 271-5.

Kankare, J. (1998). Opertive treatment of displaced intra-articular fractures of the calcaneus using absorbable internal fixation: a prospective study of twenty-five fractures. *Journal of Orthopedic Trauma*, 12(6), 413-9.

Kankare, J. (1997). Tibial condylar fracture fixed with totally absorbable, self-reinforced polyglycolide screws. A preliminary report. *Archives of Orthopedic Trauma Surgery*, 116(3), 133-6.

Kaplan, B., Hoard, M., & Park, S. (2001). Immediate mobilization following fixation of mandible fractures: a prospective, randomized study. *Laryngscope*, 111(9), 1520-4.

Kapukaya, A., Subasi, M., Necmioglu, S., & Arsian, H. (1998). Treatment of closed femoral diaphyseal fractures with external fixators in children. *Archives of Orthopedic Trauma Surgery*, 117(6-7), 387-9.

Karladani, A., Granhed, H., Edshage, B., & Jerre, R. (2000). Displaced tibial shaft fractures: a prospective randomized study of closed intramedullary nailing versus cast treatment in 53 patients. *Acta Orthopedic Scandinavian*, 71(2), 160-7.

Kawaguchi, S., Sawada, K., Nabeta, Y., & Hayakawa, M. (1998). Recurrent dorsal angulation of the distal radius fracture during dynamic external fixation. *Journal of Hand Surgery*, 23(5), 920-5.

Keating, J., O'Brien, P., Blachut, P., & Meek, R. (1997). Locking intramedullary nailing with and without reaming for open fractures of the tibial shaft. A prospective, randomized study. *Journal of Bone and Joint Surgery*, 79(3), 334-41.

Keener, J., Parsons, B., Flatow, E., & Rogers, K. (2007). Outcomes after percutaneous reduction and fixation of proximal humeral fractures. *Journal of Shoulder and Elbow Surgery*, 16(3), 330-8.

Kennedy, J., Harty, J., Casey, K., & Jan, W. (2003). Outcome after single technique ankle arthrodesis in patients with rheumatoid arthritis. *Clinical Orthopedics and Related Research*, 412, 131-8.

Kenwright, J., Richardson, J., Goodship, A., & Evans, M. (1986). Effect of controlled axial micromovement on healing of tibial fractures. *Lancet*, 22(2), 1185-7.

Keret, D., Bollini, G., Dungl, P., & Fixsen, J. (2000). The fibula in congenital pseudoarthrosis of the tibia: the EPOS multicenter study. European Paediatric Orthopaedic Society (EPOS). *Journal of Pediatric Orthopedics*, 9(2), 69-74.

Kershaw, C., Cunningham, J., & Kenwright, J. (1993). Tibial external fixation, weight bearing, and fracture movement. *Clinical Orthopedics and Related Research*, 293, 28-36.

Khanduja, V., Lim, C., Vemulapalli, K., Lee, C. (2006). Detachable functional focused rigidity cast for metatarsal fractures. *British Journal of Nursing*, 15(5), 282-4.

Kitoka, H., Schaap, E., Chao, E.,& An, K. (1994). Displaced intra-articular fractures of the calcaneous treated non-operatively. Clinical results and analysis of motion and ground-reaction and temporal forces. *Journal of Bone and Joint Surgery*, 76(10), 1531-40.

Knapp, D., Jones, E., Blanco, J., & Flynn, J. (2005). Allograft bone in spinal fusion for adolescent idiopathic scoliosis. *Journal of Spinal Disorders and Technology*, 18, 73-6.

Konrad, G., Markmiller, M., Lenich, A., & Mayr, E. (2005). Tourniquets may increase postoperative swelling and pain after internal fixation of ankle fractures. *Clinical Orthopedics and Related Research*, 433, 189-94.

Kopylov, P., Aspendberg, P., Yuan, X., & Ryd, L. (2001). Radiostereometric analysis of distal radial fracture displacement during treatment: a randomized study comparing Norian SRS and external fixation in 23 patients. *Acta Orthopedic Scandinavian*, 72(1), 57-61.

Kopylov, P., Runggvist, K., Jonsson, K., & Aspenberg, P. (1999). Norian SRS versus external fixation in redisplaced distal radial fractures. A randomized study in 40 patients. *Acta Orthopedics Scandinavian*, 70(1), 1-5.

Kornblum, M., Fischgrund, J., Herkowitz, H., & Abraham, D. (2004). Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective long-term study comparing fusion and pseudarthrosis. *Spine*, 29(7), 733-4.

Koshimune, M., Kamano, M., Takamatsu, K., & Ohashi, H. (2005). A

randomized comparison of locking and non-locking palmar planting for the unstable Colles' fractures in the elderly. *Journal of Hand Surgery*, 30(5), 499-501.

Kosygan, K., Mohan, R., & Newman, R. (2002). The Gotfried percutaneous the fixation of intertrochanteric fractures of the hip. *Journal of Bone and Joint Surgery*, 84(1), 19-22.

Koval, K. (2001). Preoperative skin treaction was not useful for hip fractures. *Journal of Bone and Joint Surgery*, 83(2), 303.

Kozin, S., & Bishop, A. (1994). Tension wire fixation of avulsion fractures at the thumb metacarpophalangeal joint. *Journal of Hand Surgery*, 19(6), 1027-31.

Kreder, H., Agel, J., McKee, M., & Schemitsch, E. (2006). A randomized, controlled trial of distal radius fractures with metaphyseal displacement but without joint incongruity: closed reduction and casting versus closed reduction, spanning external fixation, and optional percutaneous K-wires. *Journal of Orthopedic Trauma*, 20(2), 115-21.

Krettek, C., Konemann, B., Miclau, T., & Schandelmaier, P. (1997). A new technique for the distal locking of solid AO unreamed tibial nails. *Journal of Orthopedic Trauma*, 11(6), 446-51.

Kuklo, T., Potter, B., Lenke, L., & Polly, D. (2007). Surgical revision rates of hooks verses hybrid versus screws versus combined anteroposterior spinal fusion for adolescent idiopathic scoliosis. *Spine*, 32(20), 2258-64.

Kuklo, T., Bridwell, K., Lewis, S., & Baldus, C. (2001). Minimum 2-year analysis of sacropelvic fixation and L5-S1 fusion using S1 and iliac screws. *Spine*, 26(18), 1976-83. SO:Spine

Lamberg, T., Remes, V., Helenius, I., & Schlenzka, I. (2005). Long-term clinical, functional and radiological outcome 21 years after posterior or posterolateral fusion in childhood and adolescence isthmic spondylolisthesis. *European Spine Journal*, 14(7), 639-44.

Larsen, L., Madsen, J., Hoiness, P., & Ovre, S. (2004). Should insertion of intramedullary nails for tibial fractures be with or without reaming? A prospective, randomized study with 3.8 years' follow-up. *Journal of Orthopedic Trauma*, 18(3), 144-9.

Lee, F., Sincopi, S., Lee, F., & Vital, M. (2006). Treatment of congenital

pseudarthrosis of the tibia with recombinant human bone morphogenetic protein-7 (rhBMP-7). A report of five cases. *Journal of Bone and Joint Surgery*, 88(3), 627-33.

Lei, H., & Yi, L. (1998). One-stage open cancellous bone grafting of infected fracture and nonunion. *Journal of Orthopedic Science*, 3(6), 318-23.

Leung, K., Lee, W., Tsui, H., & Liu, P. (2004). Complex tibial fracture outcomes following treatment with low-intensity pulsed ultrasound. *Ultrasound Medicine Biology*, 30(3), 389-95.

Leung, F., & Chow, S. (2003). A prospective, randomized trial comparing the limited contact dynamic compression plate with the point contact fixator for forearm fractures. *Journal of Bone and Joint Surgery*, 85(12), 2343-8.

Lin, J. (2006). Effectiveness of locked nailing for the displaced three-part proximal humeral fractures. *Journal of Trauma*, 61(2), 363-74.

Lindahl, O. (1984). Survey of orthopedic surgical research in university center. *Clinical Orthopedic and Related Research*, 191, 136-8.

Lindquist, S., Malmgvist, B., & Ullmark, G. (1989). Fixation of femoral neck fractures. Prospective comparison of von Bahr screws, Gouffon screws, and Hessel pins. *Acta Orthopedic Scandinavian*, 60(3), 293-8.

Linovitz, R., Pathria, M., Bernhardt, M., & Green, D. (2002). Combined magnetic fields accelerate and increase spine fusion: a double-blind, randomized, placebo controlled study. *Spine*, 27(13), 1383-9.

Lonner, J., Koval, K., Golyakhovsky, V., & Frankel, V. (1995). Posttraumatic nonunion of the distal tibial metaphysis. Treatment using the Ilizarov circular external fixator. *American Journal of Orthopedics*, Supplement, 16-21.

Luna Gonzalez, F., Lopez ArEvalo, R., Meschian Coretti, S., & Urbano Labajos, V. (2005). Pulsed electromagentic stimulation of regenerate bone in lengthening procedures. *Acta Orthopaedica Belgica*, 71(5), 571-6.

Lyritis, G., & Johnell, O. (1993). Orthopaedic management of hip fracture. *Bone*, Suppl, 11-17.

Mandronero, A., Pitillas, I., & Manso, F. (1988). Pulsed electromagnetic field treatment failure in radius non-united fracture healing. *Journal of Biomedical Engineering*, 10(5), 463-6.

Madsen, J., Naess, L., Aune, A., & Alho, A. (1998). Dynamic hip screw with

trochanteric stabilizing plate in the treatment of unstable proximal femoral fractures: a comparative study with the Gamma nail and compression hip screw. *Journal of Orthopedic Trauma*, 12(4), 241-8.

Madsen, F., Linde, E., Andersen, E., Birke, H., & Havass, I. (1987). Fixation of displaced femoral neck fractures. A comparison between sliding screw plate and four cancellous bone screws. *Acta Orthopedic Scandinavian*, 58(3), 212-6.

Mammi, G., Rocchi, R., Cadossi, R., & Massari, L. (1993). The electrical stimulation of tibial osteotomies. Double-blind study. *Clinical Orthopedics and Related Research*, 288, 246-54.

Maneerit, J., Meknavin, S., & Hanpanitkitkan, S. (2004). Percutaneous versus open bone grafting in the treatment of tibial fractures: a randomized prospective trial. *Journal of Medicine Association Thai*, 87(9), 1034-40.

Marchetti, P., Vicenzi, G., Impallomeni, C., & Landi, S. (2000). The use of elastic nails for intramedullary fixation of humeral fractures and nonunions. *Orthopedics*, 23(4), 343-7.

Markmiller, M., Tjarksen, M., Mayr, E., & Ruter, A. (2000). The unreamed tibia nail. Multicenter study of AO/ASIF. Osteosynthesefragen/Association for the Study of Internal Fixation. *Langenbecks Archive of Surgery*, 385(4), 276-83.

Marsh, J., Muehling, V., Dirschl, D., & Hurwitz, S. (2006). Tibial plafond fractures treated by articulated external fixation: a randomized trial of postoperative motion versus nonmotion. *Journal of Orthopedic Trauma*, 20(8), 536-41.

Marsh, J., Bonar, S., Nepola, J., & Decoster, T. (1995). Use of an articulated external fixation for fractures of the tibial plafond. *Journal of Bone and Joint Surgery*, 77(10), 1498-501.

Mattsson, P., & Larsson, S. (2003). Stability of internally fixed femoral neck fractures augmented with resorbable cement. A prospective randomized study using radiostereometry. *Scandanavian Journal of Surgery*, 92(3), 215-9.

Mazda, K., Khairouni, A., Pennecot, G., & Bensahel, H. (1997). Closed flexible intramedullary nailing of the femoral shaft fractures in children. *Journal of Pediatric Orthopedics*, 6(3), 198-202.

McAndrew, M., Gorman, P., & Lange, T. (1988). Tricalcium phosphate as a bone

graft substitute in trauma: preliminary report. *Journal of Orthopedic Trauma*, 2(4), 333-9.

McGuire, R., & Amundson, G. (1993). The use of primary internal fixation in spondylolisthesis. *Spine*, 18(12), 1662-72.

McLauchlan, G., Cowan, B., Annan, I., & Robb, J. (2002). Management of completely displaced metaphyseal fracture of the distal radius in children. A prospective, randomized controlled trial. *Journal of Bone and Joint Surgery*, 84(3), 413-7.

McQueen, M., Hajducka, C., & Court-Brown, C. (1996). Redisplaced unstable fractures of the distal radius: a prospective randomized comparison of four methods of treatment. *Journal of Bone and Joint Surgery*, 78(3), 404-9.

Merloz, P., Tonetti, J., Pittet, L., Coulomb, M., & Lavellee, S. (1998). Computer-assisted spine surgery. *Computer Aided Surgery*, 3(6), 297-305.

Mills, W., Chapman, J., Robinson, L., & Slimp, J. (2000). Somatosensory evoked potential monitoring during closed humeral nailing: a preliminary report. *Journal of Orthopedic Trauma*, 14(3), 167-70.

Moed, B., Subramanian, S., van Holsbeeck, M., & Watson, J. (1998). Ultrasound for the early diagnosis of tibial fracture healing after interlocked nailing without reaming: clinical results. *Journal of Orthopedic Trauma*, 12(3), 206-13.

Mologne, T., Lundeen, J., Clapper, M., & O'Brien, T. (2005). Early screw fixation versus casting in the treatment of acute Jones fractures. *American Journal of Sports Medicine*, 33(7), 970-5.

Mooney, V. (1990). A randomized double-blind prospective study of the efficacy of pulsed electromagnetic fields for interbody lumbar fusions. *Spine*, 15(7), 708-12.

Moorcroft, C., Thomas, P., Ogrodnik, P., & Verborg, S. (2000).A device for improved reduction of tibial fractures with external fixation. *Proc Inst Med Eng*, 214(5), 449-57.

Moore, J., Shank, J., Morgan, S., & Smith, W. (2006). Syndesmosis fixation: a comparison of three and four cortices of screw fixation without hardware removal. *Foot and Ankle International*, 27(8), 567-72.

Moroni, A., Faldini, C., Hoang-Kim, A., & Pegreffi, F. (2007).Alendronate improves screw fixation in osteoporotic bone. *Journal of Bone and Joint Surgery*, 89(1), 96-101.

Moroni, A., Faldini, C., Pegreffi, F., & Giannini, S. (2004). HA-coated screws decrease the incidence of fixation failure in osteoporotic trochanteric fractures. *Clinical Orthopedics and Related Research*, 425, 87-92.

Muldoon, M., Padgett, D., Sweet, D., & Deuster, P. (2001). Femoral neck stress fractures and metabolic bone diseases. *Journal of Orthopedic Trauma*, 15(3), 181-5.

Munk, B., Fokjaer, L., Larsen, C., & Johannsen, H. (1995). Diagnosis of scaphoid fractures. A prospective multicenter study of 1,052 patients with 106 fractures. *Acta Orthopedic Scandinavian*, 66(4), 359-60.

Musialek, J., Fillip, P., & Nieslanik, J. (1998). Titanium-nickel shape memory clamps in small bone surgery. *Archive of Orthopedics and Trauma Surgery*, 1217(6-7),341-4. SO:Arch Orthop Trauma Surg

Nand, S., Sengar, G., Nand, S., Jain, V., & Gupta, T. (1996). Dual use of silver for management of chronic bone infections and infected non-unions. *Journal of Indian Medical Association*, 94(3), 91-5.

Nassif, J., Gorczyca, J., Cole, J., & Pugh, K. (2000). Effect of acute reamed versus unreamed intramedullary nailing on compartment pressure when treating closed tibial shaft fractures: a randomized prospective study. *Journal of Orthopedic Trauma*, 14(8), 554-8.

Noordeen, M., Lavy, C., Shergill, N., & Tuite, J. (1995). Cyclical micromovement and fracture healing. *Journal of Bone and Joint Surgery*, 77(4), 645-8.

Oda, H., Nakamura, K., Matsushita, T., & Yamamoto, S. (2006). Clincial use of a newly developed calcium phosphate cement. *Journal of Orthopedic Science*, 11(2), 167-74.

Odvina, C., Zerwekh, J., Rao, D., & Maalouf, N. (2005). Severely suppressed bone turnover: a potential complication of alendronate therapy. *Journal of Clinical Endocrinology Metabolism*, 90(3), 1294-301.

Oh, C., Park, B., Inh, J.,& Kyung, H. (2000). Fracture separation of the distal humeral epiphysis in children younger than three years old. *Journal of Pediatric Orthopedics*, 20(2), 173-6.

Ohnishi, I., Sato, W., Matsuyaman, J., & Yajima, H. (2005). Treatment of congenital pseudarthrosis of the tibia: a multicenter study in Japan. *Journal of Pediatric Orthopedics*, 25(2), 219-24.

OlaOlorun, D., Oladiran, I., & Adeniran, A. (2001). Complications of fracture treatment by traditional bonesetters in southwest Nigeria. *Family Practice*, 18(6), 635-7.

Olerud, C., Rehnberg, L., & Hellquist, E. (1991). Internal fixation of femoral neck fractures. Two methods compared. *Journal of Bone and Joint Surgery*, 73(1), 16-9.

Onuminya, J. (2006). Performance of a trained traditional bonesetter in primary fracture care. *South Africa Medical Journal*, 96(4), 320-2.

Oransky, M., & Gasparini, G. (1997). Associated lumbosacral junction injuries (LSJIs) in pelvic fractures. *Journal of Orthopedic Trauma*, 11(7), 509-12.

Ostermann, P., Ekkernkamp, A., Henry, S., & Muhr, G. (1994). Bracing of stable shaft fractures of the ulna. *Journal of Orthopedic Trauma*, 8(3), 245-8.

Panozzo, A., Manfrini, M., & Capanna, R. (1996). Effect of electromagnetic fields on patients undergoing massive bone graft following bone tumor resection. *Journal of Bone and Joint Surgery*, 78(2-3), 133.

Pape, H., Rixen, D., Morley, J., & Husebye, E. (2007). Impact of the method of initial stabilization for femoral shaft fractures in patients with multiple injuries at risk for complications (borderline patients). *Annals Surgery*, 246(3), 299-501.

Parker, M., Raghavan, R., & Gurusamy, K. (2007). Incidence of fracture-healing complications after femoral neck fractures. *Clinical Orthopedics and Related Research*, 458, 175-9.

Partio, E., Tumpo, P., Hirvensalo, E., & Bostman, O. (1997). Totally absorbable fixation in the treatment of fractures of the distal femoral epiphyses. A prospective clinical study. *Archives of Orthopedic and Trauma Surgery*, 116(4), 213-6.

Partio, E., Hirvensalo, E., Bostman, O., & Rokkanen, P. (1996). A prospective controlled trial of fracture of the humeral medial epicondyle--how to treat? *Annales chirurgiae et gynaecologiae*, 85(1), 67-71.

Patel, A., Ricci, W., McDonald, D., & Borrelli, J. (2006). Treatment of periprosthetic femoral shaft nonunion. *Journal of Arthroplasty*, 21(3), 435-43.

Poeisson, A., Vavruch, L., & Hedlund, R. (2007). Long-term randomized comparison between a carbon fiber cage and the Cloward procedure in the cervical spine. *European Spine Journal*, 16(2), 173-8.

Petersen, M., Lauritzen, J., Schwarz, P., & Lund, B. (1998). Effect of nasal salmon calcitonin on post-traumatic osteopenia following ankle fracture. A randomized double-blind placebo-controlled study in 24 patients. *Acta Orthopedic Scandinavian,* 69(4), 347-50.

Pfeiffer, B., Nubling, M., Siebert, H., & Schadel-Hopfner, M. (2006). A prospective multi-center cohort study of acute non-displaced fractures of the scaphoid: operative versus non-operative treatment. *BMC Musculoskeletal Disorders,* 11, 41.

Pflugmacher, R., Beth, P., Schroeder, R., & Schaser, K. (2007). Balloon kyphoplasty for the treatment of pathological fractures in the thoracic and lumbar spine caused by metastasis: one-year follow-up. *Acta Radiol,* 48(1), 89-95.

Plecko, M., & Kraus, A. (2005). Internal fixation of proximal humerus fractures using the locking proximal humerus plate. *Oper Orthop Traumatol,* 17(1), 25-50.

Popovic, N., Gillet, P., Rodriguez, A., & Lemaire, R. (2000). Fracture of the radial head with associated elbow dislocation: results of treatment using a floating radial head prosthesis. *Journal of Orthopedic Trauma,* 14(3), 171-7.

Porter, K., & Davies, J. (1986). The control of pain after Keller's procedure--a controlled double blind prospective trail with local anesthetic and placebo. *Ann R Coll Surg Engl,* 67(5), 293-4. SO:Ann R Coll Surg Engl

Prince, R., Sipos, A., Hossain, A., & Syverson, U. (2005). Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. *Journal of Bone and Mineral Research,* 20(9), 1507-13.

Prichett, J. (1993). Rush rods versus plate osteosyntheses for unstable ankle fractures in the elderly. *Orthopedics Review,* 22(6), 691-6.

Prokop, A., Helling, H., Hahn, U., & Udomkaewkanjana, C. (2005). Biodegradable implants for Pipkin fractures. *Clinical Orthopedics and Related Research,* 432, 226-33.

Rajasekhar, C., Ray, P., & Bhamra, M. (2001). Fixation of proximal humeral fractures with the Polarus nail. *Journal of Shoulder and Elbow Surgery,* 10(1), 7-10.

Ramamurthy, C., Cutler, L., Nuttal, D., & Simison, A. (2007). The factors

affecting outcome after non-vascular bone grafting and internal fixation for the nonunion of the scaphoid. *Journal of Bone and Joint Surgery*, 89(5), 627-32.

Randelli, P., Landi, S., Fanton, F., & Hoover, G. (1999). Treatment of ipsilateral femoral neck and shaft fractures with the Russell-Taylor reconstructive nail. *Orthopedics*, 22(7), 673-6.

Raschke, M., Rasmussen, M., Govender, S., & Segal, D. (2007). Effects of growth hormone in patients with tibial fracture: a randomized, double-blind, placebo-controlled clinical trial. *European Journal of Endocrinology*, 156(3), 341-51.

Rebuzzi, E., Pannone, A., Schiavetti, S., & Santoriello, P. (2002). IMHS clinical experience in the treatment of peritrochanteric fractures. The results of a multicentric Italian study of 981 cases. *Injury*, 33(5), 407-12.

Rehnberg, L., & Olerud, C. (1989). Fixation of femoral neck fractures. Comparison of the Uppsala and von Bahr screws. *Acta Orthop Scand*, 60(5), 579-84.

Reilly, T., Sasso, R., & Hall, P. (2003). Atlantoaxial stabilization: clinical comparison of posterior cervical wiring technique with transarticular screw fixation. *Journal of Spinal Disorders and Techniques*, 16(3), 248-53.

Richards, P., Kurta, I., Jasani, V., Jones, C., & Rahmatalla, A. (2007). Assessment of CAOS as a training model in spinal surgery: a randomized study. *European Spine Journal*, 16(2), 239-44.

Richter, D., Ostermann, P., Ekkernkamp, A., & Muhr, G. (1998). Elastic intramedullary nailing: a minimally invasive concept in the treatment of unstable forearm fractures in children. *Journal of Pediatric Orthopedics*, 18(4), 457-61.

Riedel, G., & Valentin-Opran, A. (1999). Clinical evaluation of rhBMP-2/ACS in orthopedic trauma: a progress report. *Orthopedics*, 22(7), 663-7.

Riemer, B., Miranda, M., Butterfield, S., & Burke, C. (1995). Nonreamed nailing of closed and minor open tibial fractures in patients with blunt polytrauma. *Clinical Orthopedics and Related Research*, 320, 199-24.

Rikli, D., Businger, A., & Babst, R. (2005). Dorsal double-plate fixation of the distal radius. *Oper Orthop Traumatol*, 17(6), 624-40.

Ring, D., Jupiter, J., Brennwald, J., & Buchler, U. (1997). Prospective multicenter

trial of a plate for dorsal fixation of distal radius fractures. *Journal of Hand Surgery*, 22(5), 777-84.

Ristiniemi, J., Flinkkila, T., Hyvonen, P., & Lakovaara, M. (2007). RhBMP-7 accelerates the healing in distal tibial fractures treated by external fixation. *Journal of Bone and Joint Surgery*, 89(2), 265-72.

Rodriguez-Merchan, E., & Galindo, E. (1999). Intra-articular displaced fractures of the calcaneus. Operative vs. non-operative treatment. *International Orthopedics*, 23(1), 63-5.

AU:Rodriguez-Merchan, E. (1995). Compression plating versus hackethal nailing in closed humeral shaft fractures failing nonoperative reduction. *Journal of Orthopedic Trauma*, 9(3), 194-7.

Roland, N., Hughes, J., Daley, M., & Cook, J. (1993). Electromagnetic stimulation as treatment of tinnitus: a pilot study. *Clinical Otolaryngology and Allied Sciences*, 18(4), 278-81.

Romanus, B., Bollini, G., Dungl, P., & Fixsen, J. (2000). Free vascular fibular transfer in congenital pseudoarthrosis of the tibia: results of the EPOS multicenter study. European Pediatric Orthopedic Society (EPOS). *Journal of Pediatric Orthopedics*, 9(2), 90-3.

Rompe, J., Rosendahl, T., Schollner, C., & Theis, C. (2001). High-energy extracorporeal shock wave treatment of nonunions. *Clinical Orthopedics and Related Research*, 387, 102-111.

Saarenpaa, I., Haikkinen, T., & Jalovaara, P. (2007). Treatment of subtrochanteric fractures. A comparison of the Gamma nail and the dynamic hip screw: short-term outcome in 58 patients. *International Orthopedics*, 31(1), 65-70.

Sadowski, C., Lubbeke, A., Saudan, M., & Riand, N. (2002). Treatment of reverse oblique and transverse intertrochanteric fracture with use of an intramedullary nail or a 95 degrees screw-plate: a prospective, randomized study. *Journal of Bone and Joint Surgery*, 84(3), 372-81.

Safoury, Y. (1999). Use of reversed-flow vascularized pedicle fibular graft for treatment of nonunion of the tibia. *Journal of Reconstruction Microsurgery*, 15(1), 23-8.

Sakamoto, K., Nakamura, T., Hagino, H., & Endo, N. (2006). Report on the Japanese Orthopaedic Association's 3- year project observing hip fractures at fixed-point hospitals. *Journal of Orthopedic Science*, 11(2), 127-34.

Sarda, L., Cremieux, A., Lebellec, Y., & Meulemans, A. (2003). Inability of 99mTc-ciprofloxacin scintigraphy to discriminate between septic and sterile osteoarticular diseases. *Journal of Nuclear Medicine*, 44(6), 920-6.

SattarSyed, A., Islam, M., Rabbani, K., & Talukder, M. (1999). Pulsed Electromagnetic Fields for the Treatment of Bone Fractures. *Bangladesh Med Res Counc Bull*, 25(1), 6-10.

Satter Syed, A., Islam, M., Rabbani, K., & Talukder, M. (1999). Pulsed electromagnetic fields for the treatment of bone fractures. *Bangladesh Med Res Counc Bull*, 25(1), 6-10.

Saxena, A., DiDomenico, L., Widtfeldt, A., & Adams, T. (2005). Implantable electrical bone stimulation for arthrodeses of the foot and ankle in high-risk patients: a multicenter study. *Journal of Foot and Ankle Surgery*, 44(6), 450-4.

Scheerlinck, T., & Handelberg, F. (2002). Functional outcome after intramedullary nailing of humeral shaft fractures: comparison between retrograde Marchetti-Vicenzi and unreamed AO antegrade nailing. *Journal of Trauma*, 53(2), 60-71.

Schildhauer, T., Ledoux, W., Chapman, J., & Henley M. (2003). Triangular osteosynthesis and iliosacral screw fixation for unstable sacral fractures: a cadaver and biomechanical evaluation under cyclic loads. *Journal of Orthopedic Trauma*, 17(1), 22-31.

Schmalholz, A. (1989). Bone cement for redislocated Colles' fracture. A prospective comparison with closed treatment. *Acta Orthop Scand*.60(2), 212-7.

Schmiedt, C., Lu, Y., Heaney, K., & Muir, P. (2007). Comparison of two doses of bone healing in dogs. *Am J Vet Res*, 68(8), 834-40.

Schuind, F., Haentjents, P., Van Innis, F., & Vander Maren, C. (1999). Prognostic factors in the treatment of carpal scaphoid nonunions. *Journal of Hand Surgery*, 24(4), 761-76.

Schwarz, N., Posch, E., Mayr, J., & Fischmeister, F. (1998). Long-term results of unstable pelvic ring fractures in children. *Injury*, 29(6), 431-3.

Segur, J., Torner, P., Garcia, S., & Combalia, A. (1998). Use of bone allograft in tibial plateau fractures. *Archives of Orthopedics and Trauma Surgery*, 117(6-7), 357-9.

Seide, K., Weinrich, N., Wenzi, M., & Wolter, D. (2004). Three-dimensional load measurements in an external fixator. *Journal of Biomechanics*, 37(9).

Selvakumar, K., Saw, K., & Fathima, M. (2001). Comparison study between reamed and unreamed nailing of closed femoral fractures. *Medical Journal of Malaysia*, 56, 24-8.

Sernbo, I., Holmguist, H., Redlund-Johnell, I.,& Johnell, O. (1994). Radiographic prediction of failure after fixation of cervical hip fractures. *Acta Orthop Scand*, 65(3), 295-8.

Shepherd, L., Shean, C., Gelalis, I., & Lee, J. (2001). Prospective randomized study of reamed versus unreamed femoral intramedullary nailing: an assessment of procedures. *Journal of Orthopedic Trauma*,15(1), 28-32.

Siambanes, D., & Miz, G. (1998). Treatment of symptomatic anterior cervical nonunion using the Rogers interspinous wiring technique. *American Journal of Orthopedics*, 27(12), 792-6.

Siebenrock, K., Gautier, E., Ziran, B., & Ganz, R. (1998). Trochanteric flip osteotomy for cranial extension and muscle protection in acetabular fracture fixation using a Kocher-Langenbeck approach. *Journal of Orthopedic Trauma*, 12(6), 387-91.

Simmons, J., Mooney, V., & Thacker, I. (2004). Pseudarthrosis after lumbar spine fusion: nonoperative salvage with pulsed electromagnetic fields. *American Journal of Orthopedics*, 33(1), 27-30.

Siris, E., Harris, S., Easteli, R., & Zanchetta, J. (2005). Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. *Journal of Bone and Mineral Research*, 20(9), 1514-24.

Skoff, H. (1995). Bone marrow/allograft component therapy. A clinical trail. *American Journal of Orthopedics*, 24(1), 40-7.

Smith, W., Ziran, B., Agudelo, J., & Morgan, S. (2006). Expandable intramedullary nailing for tibial and femoral fractures: a preliminary analysis of perioperative complications. *Journal of Orthopedic Trauma*, 20(5), 310-4.

Sochart, D. (1998). Poor results following internal fixation of displaced subcapital femoral fractures: complacency in fracture reduction. *Archives of Orthopedic and Trauma Surgery*, 117(6-7), 379-82.

Sommer, C., Gautier, E., Muller, M., & Helfet, D. (2003). First clinical results of

the Locking Compression Plate (LCP). *Injury*, 34(2), 43-54.

Sonne-Holm, S., Nordkild, P., Dyrbye, M., & Jensen, J. (1987). The predictive value of bone scintigraphy after internal fixation of femoral neck fractures. *Injury*,19(1), 33-5.

Sorger, J., Kirk, P., Ruhnke, C., Bjornson, S., & Levy, M. (1999). Once daily, high dose versus divided, low dose gentamicin for open fractures. *Clinical Orthopedics and Related Research*, 366, 197-204.

Stancic, M., Gregorovic, E., Nozica, E., & Penezic, L. (2001). Anterior decompression and fixation versus posterior reposition and semirigid fixation in the treatment of unstable burst thoracolumbar fracture: prospective clinical trial. *Croatia Medical Journal*, 42(1), 49-53.

Steffensen, B., Caffesse, R., Hanks, C., & Avery, J. (1988). Clinical effects of electromagentic stimulation as an adjunct to periodontal therapy. *Journal of Periodontology*, *59*(1), 46-52.

Stoffeien, D., & Broos, P. (1998). Minimally displaced distal radius fractures: do they need plaster treatment? *Journal of Trauma*,44(3), 503-5.

Strohm, P., Muller, C., Boll, T., & Pfister, U. (2004). Two procedures for kirschner wire osteosynthesis of distal radial fractures. A randomized trial. *Journal of Bone and Joint Surgery*, 86-12, 2621-8.

Sweet, F., Lanke, L., Bridwell, K., & Blanke, K. (2001). Prospective radiographic and clinical outcomes and complications of single solid rod instrumented anterior spinal fusion in adolescent idiopathic scoliosis. *Spine*, 26(18), 1956-65.

Swiontkowski, M., Aro, H., Donell, S., & Esterhal, J. (2006). Recombinant human bone morphogenetic protien-2 in open tibial fractures. A subgroup analysis of data combined from two prospective randomized studies. *Journal of Bone and Joint Surgery*, 88(6), 1258-65.

Szivek, J., Roberto, R., Slack, J., & Majeed, B. (2002). An implantable strain measurement system designed to detect spine fusion: preliminary results from a biomechanical in vivo study. *Spine*, 27(5), 487-97.

Tejano, N., Puno, R., & Ignacio, J. (1996). The use of implantable direct current stimulation in multilevel spinal fusion without instrumentation. A prospective clinical and radiographic evaluation with long-term follow-up. *Spine*, 21(16), 1904-8.

Tengstrand, B., Cederholm, T., Sodergvist, A., & Tidermark, J. (2007). Effects of

protien-rich supplementation and nandrolone on bone tissue after a hip fracture. *Clinical Nutrition,* 26(4), 406-5.

Thalgott, J., Sasso, R., Cotler, H., & Aebi, M. (1997). Adult spondylolisthesis treated with posterolateral lumbar fusion and pedicular instrumentation with AO DC plates. *Journal of Spinal Disorder,* 10(3), 204-8.

Tidermark, J., Ponzer, S., Carlsson, P., & Sodergvist, A. (2004). Effects of protein-rich supplementation and nandrolone in lean elderly women with femoral neck fractures. *Clinical Nutrition,* 23(4), 587-96.

Tidermark, J., Ponzer, S., Svensson, O., & Sodegvist, A. (2003). Internal fixation compared with total hip replacement for displaced femoral neck fractures in the elderly. a randomised, controlled trial. *Journal of Bone and Joint Surgery,* 85(3), 380-8.

Tidermark, J., Zethraeus, N., Svensson, O., Tornkvist, H., & Ponzer, S. (2002). Quality of life related to fracture displacement among elderly patients with femoral neck fractures treated with internal fixation. *Journal of Trauma,* 16(1), 34-8.

Tomaino, M., King, J., & Pizillo, M. (2000). Correction of lunate malalignment when bone grafting scaphoid nonunion with humpback deformity: rationale and results of a technique revisited. *Journal of Hand Surgery,* 25(2), 322-9.

Tomic, S., Bumbasirevic, M., Lesic, A., & Bumbasirevic, V. (2006). Modification of the Ilizarov external fixator for aseptic hypertrophic nonunion of the clavical: an option for treatment. *Journal of Orthopedic Trauma.*20(2), 122-8.

Tornetta, P., & Tiburzi, D. (1997). The treatment of femoral shaft fractures using intramedullary interlocked nails with and without intramedullary reaming: a preliminary report. *Journal of Orthopedic Trauma,* 11(2), 89-92.

Tornetta, P., Bergman, M., Watnik, N., & Berkowitz, G. (1994). Treatment of grade-IIIb open tibial fractures. A prospective randomised comparison of external fixation and non-reamed locked nailing. *Journal of Bone and Joint Surgery,* 76(1), 13-9.

Trock, D., Bollet, A., Dyer, R., Fielding, L., Miner, W., & Markoll, R. (1993). A double-blind trial of the clinical effects of pulsed electromagnetic fields in osteoarthritis. *Journal of Rheumatology,* 20(3), 456-60.

Tu, Y., Lin, C., Su, J., & Hsu, D. (1995). Unreamed interlocking nail versus

external fixator for open type III tibia fractures. *Journal of Trauma*, 39(2), 361-7.

Tucker, M., Schwappach, J., Leighton, R., Coupe, K., & Ricci, W. (2007). Results of femoral intramedullary nailing in patients who are obese versus those who are not obese: a prospective multicenter comparison study. *Journal of Orthopedic Trauma*, 21(8), 523-9.

Tudisco, C., Bollini, G., Dungl, P., & Fixen, J. (2000). Functional results at the end of skeletal growth in 30 patients affected by congenital pseudoarthrosis of the tibia. *Journal of Pediatric Orthopedics*, 9(2), 94-102.

Uhlin, B., & Hammer, R. (1998). Attempted unreamed nailing in tibial fractures: a prospective consecutive series of 55 patients. *Acta Orthopedic Scandanavian*, 69(3), 301-5.

Upadhyay, A., Jain, P., Mishra, P., & Maini, L. (2004). Delayed internal fixation of fractures of the neck of the femur in young adults. A prospective, randomized study comparing close and open reduction. *Journal of Bone and Joint Surgery*, 86(7), 1035-40.

Van der Poest Clement, E., Patka, P., Vandormael, K., & Haarman, H. (2000). The effect of alendronate on bone mass after distal forearm fracture. *Journal of Bone and Mineral Research*, 15(3), 586-93.

Van Laarhoven, C., Meeuwis, J., & van der Werken, C. (1996). Postoperative treatment of internally fixed ankle fractures: a prospective randomised study. *Journal of Bone and Joint Surgery*, 78(3), 395-9.

Van Vugt, A., Oosterwijk, W., & Goris, R. (1993). Predictive value of early scintimetry in intracapsular hip fractures. A prospective study with regard to femoral head necrosis, delayed union and non-union. *Archives of Orthopedics and Trauma Surgery*, 113(1), 33-8.

Verheyen, C., Smulders, T., & van Walsum, A. (2005). High secondary displacement rate in the conservative treatment of impacted femoral neck fractures in 105 patients. *Archives of Orthopedic and Trauma Surgery*, 125(3), 166-8.

Vinnars, B., Ekenstam, F., & Gerdin, B. (2007). Comparison of direct and indirect costs of internal fixation and cast treatment in acute scaphoid fractures: a randomized trial involving 52 patients. *Acta Orthopedics*, 78(5), 672-9.

Wada, T., Usui, M., Isu, K., & Yamawakii, S. (1999). Reonstruction and limb

salvage after resection for malignant bone tumor of the proximal humerus. A sling procedure using a free vascularised fibular graft. *Journal of Bone and Joint Surgery*, 81(5), 808-13.

Waikakul, S., Harnroongroj, T., & Vanadurongwan, V. (1999). Immediate stabilization of unstable pelvic fractures versus delayed stabiliztation. *Journal of Medical Association Thai*, 82(7), 637-42.

Waikakul, S., Sakkarnkosol, S., & Vanadurongwan, V. (1998). Vascular injuries in compound fractures of the leg with initially adequate circulation. *Journal of Bone and Joint Surgery*, 80(2), 254-8.

Wallny, T., Sagebiel, C., Westerman, K., & Wagner, U. (1997). Comparative results of bracing and interlocking nailing in the treatment of humeral shaft fractures. *International Orthopedics*, 21(6), 374-9.

Wang, C., Chen, H., Chen, C., & Yang, K. (2001). Treatment of nonunions of long bone fractures with shock waves. *Clinical Orthopedics and Related Research*, 387, 95-101.

Wang, C., Liu, H., & Fu, T. (2007). The effects of extracorporeal shockwave on acute high-energy long bone fractures of the lower extremity. *Archives of Orthopedic and Trauma Surgery*, 127(2), 137-42.

Watson, J., Moed, B., Cramer, K., & Karges, D. (1998). Comparison of the compression hip screw with the Medoff sliding plate for intertrochanteric fractures. *Clinical Orthopedics and Related Research*, 348, 79-86.

Weber, D., & Peter, R. (1999). Distal femoral fractures after knee arthroplasty. *International Orthopedics*, 23(4), 236-9.

Wei, S., Born, C., Abene, A., Ong, A., & Hayda, R. (1999). Diaphyseal forearm fractures treated with and without bone graft. *Journal of Trauma*, 46(6), 1045-8.

Weiss, S., Zimmermann, G., Baumgart, R., & Kasten, P. (2005). Systemic regulation of angiogenesis and matrix degradation in bone regeneration-distraction osteogenesis compared to rigid fracture healing. *Bone*, 37(6), 781-90.

Welch, W., Willis, S., & Gerszten, P. (2004). Implantable direct current stimulation in para-axial cervical arthrodesis. *Advanced Therapy*, 21(6), 389-400.

Wentz, S., Eberhardt, C., & Leonhard, T. (1999). Reconstruction plate fixation

with bone graft for mid-shaft clavicular non-union in semi-professional athletes. *Journal of Orthopedic Science*, 4(4), 269-72.

Whorton, A., & Henley, M. (1998). The role of fixation of the fibula in open fracture of the tibial shaft with fractures of the ipsilateral fibula: indications and outcomes. *Orthopedics*, 21(10), 1101-5.

Wihlborg, O. (1990). Fixation of femoral neck fractures. A four-flanged nail versus threaded pins in 200 cases. *Acta Orthopedics Scandinavian*, 61(5), 415-8.

Wilkins, R., Kelly, C., & Giusti, D. (1999). Bioassayed demineralized bone matrix and calcium sulfate: use in bone-grafting procedures. *Annales Chirugiae et Gynaecologiae*, 88(3), 180-5.

Wittwer, G., Adeyemo, W., Yerit, K., & Voracek, M. (2006). Complications after zygoma fracture fixation: is there a difference between biodegradable materials and how do they compare with titanium osteosynthesis? *Oral Surgery Oral Medicine Oral Pathology Oral Radiology*, 101(4), 419-25.

Wolfe, S., Mih, A., Hotchkiss, R., & Culp, R. (1998). Wide excision of the distal ulna: a multiecenter case study. *Journal of Hand Surgery*, 23(2), 222-8.

Wong, T., Ip, F., & Yeung, S. (2006). Comparison between percutaneous transverse fixation and intramedullary K-wires in treating closed fractures of the metacarpal neck of the little finger. *Journal of Hand Surgery*, 31(1), 61-5.

Wood, G., Boyd, R., Carothers, T., & Mansfield, F. (1995). The effect of pedicule screw/plate fixation on lumbar/lumbosacral autogenous bone graft fusions in patients with degenerative disc disease. *Spine*, 20(7), 819-30.

Wright, T. (1997). Treatment of humeral diaphyseal nonunions in patients with severely compromised bone. *Journal of South Orthopedic Association*, 6(1), 1-7.

Wu, L., Renucci, J., & Song, D. (2004). Rigid-plate fixation for the treatment of sternal nonunion. *Journal of Thoracic Cardiovascular Surgery*, 128(4), 623-4.

Wu, C. (2003).Reaming bone grafting to treat tibial shaft aseptic nonunion after plating. *Journal of Orthopedic Surgery*, 11(1), 16-21.

Wu, C., & Chen, W. (1997). Treatment of femoral shaft aseptic nonunions: comparison between closed and open bone-grafting techniques. *Journal of Trauma*, 43(1), 112-6.

Wu, C., Shih, C., Chen, W., & Tai, C. (1999). Effect of reaming bone grafting on treating femoral shaft aseptic nonunion after plating. *Archives of Orthopedic and Trauma Surgery,* 119(5-6), 303-7.

Yang, X., Fei, J., Wang, Z., Yu, H., & Sun, J. (2005). Experimental study and clinical observation of minimum-contact plate in long bone fracture. *Chinese Journal of Traumatology,* 8(2), 105-10.

Yoo, M., Cho, Y., Kim, K., & Khairuddin, M. (2006). Treatment of unstable peritrochanteric femoral fractures using 95 degrees angled blade plate. *Journal of Orthopedic Trauma,* 20(6), 687-92.

Young, C., Nanu, A., & Checketts, R. (2003). Seven-year outcome following Colles' type distal radial fracture. A comparison of two treatment methods. *Journal of Hand Surgery,* 28(5), 422-6.

Yue, J., Sontich, J., Miron, S., & Peljovich, A. (2001). Blood flow changes to the femoral head after acetabular fracture or dislocation in the acute injury and perioperative periods. *Journal of Orthopedic Trauma,* 15(3), 170-6.

Ziegenfelder, T., Hubscher, J., Abendroth, K., & Syrbe, S. (2001). Effects of differentiated stress stimuli and electromagnetic fields on bones. *Deutsche Zeitschrift fur Sportmedizin,* 52(7-8), S51.

Ziegenfelder, T., Hubscher, J., Abendroth, K., Syrbe, S., Ehrlich, S., Ndinda, T., & Gabriel, H. (2002). Effects of differentiated stimuli caused by putting weight and electromagnetic fields on bones. *International Journal of Sports Medicine,* 23S, 146S.

Ziegenfelder, T., Hubscher, J., Abendroth, K., Syrbe, S., Ehrlich, S., Ndinda, T., & Gabriel, H. (2001). Effects of differentiated stress stimuli and electromagnetic fields on bones. *Deutsche Zeitschrift fur Sportmedizin,* 52(7-8), 51.

Zoega, B., Karrholm, J., & Lind, B. (1998). One-level cervical spine fusion. A randomized study, with or without plate fixation, using radiostereometry in 27 patients. *Acta Orthopedics Scandinavian,* 69(4), 363-8.

Zollinger, P., Tuinebreijer, W., Kreis, R., & Breederveld, R. (1999). Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. *Lancet,* 354, 9195.