Low intensity ultrasound for treating fracture nonunion

and

short reviews on other bone growth stimulator devices and orthobionomics

By

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Low intensity ultrasound for treating fracture nonunion

Background

Recently, the Evidence-Based Practice Group received a request to review the effectiveness of low intensity ultrasound (c.q. Exogen®) for treating fracture nonunion.

The purpose of this review is:

- to investigate the effectiveness of low intensity ultrasound in treating patients with un-united fracture
- to investigate the characteristics of fracture nonunion patients with the potential to respond to low intensity ultrasound
- to summarize the available high level evidence on the effectiveness of other bone growth stimulator devices and orthobiologics in treating fracture nonunion

Bone, fracture healing, and fracture nonunion

Bone tissue is composed of a matrix of 25% water, 25% protein (mostly collagen) and 50% mineral salts (calcium and phosphorous salts and calcium hydroxyapatite), with a small number of bone cells spread throughout the matrix.[1] Cortical bone (compact or dense bone) provides support and resists stress. Cancellous bone (or trabecular bone) is found adjacent to the joint surfaces of bone and lining the cavity of long bones.[1]

The components of mature bone marrow, bone tissue, and periosteum have distinct composition and function. However, these components are interdependent. Bone has three mature cell types which are responsible for the production and maintenance of bone matrix. These cells are osteoblasts, osteocytes, and osteoclasts.[1-5]

Osteoblasts are derived from stem cells and progenitors, some of which are capable of forming other mesenchymal tissues such as cartilage, fat, fibrous tissue, and muscle under appropriate conditions. Osteoblasts form new bone matrix by secreting collagen fibers and initiating the calcification process. This matrix contains minerals which provide the tensile strength of the bone as well as type I collagen and other organic components which give bones flexibility. As they mature, some of the osteoblasts survive within the new matrix and develop into osteocytes. Osteocytes maintain the cellular activity of the bone. Osteoclasts are produced from stem cell populations that are derived from hematopoetic stem cells. Osteoclasts are

responsible for removing old, worn out bone matrix. Bone is a dynamic tissue that constantly replaces old bone matrix with new bone matrix.[1-5]

When bone is fractured, the blood vessels across the break are ruptured. Blood clots around the site of the fracture and forms a fracture hematoma. Because of the disrupted blood supply, many of the bone cells in the fracture site die. The fracture hematoma becomes the centre of an inflammatory response that removes cellular debris and prepares for bone tissue healing. Fracture healing is a complex process that requires recruitment of appropriate cells and subsequent expression of appropriate genes at the correct time, in the correct place.[1-5]

The first of the three predominant stages of fracture healing is the inflammatory phase. In this phase, the hematoma is formed from the blood vessels ruptured by the injury. Soon afterward, inflammatory cells invade the blood clot and initiate the lysosomal degradation of necrotic tissue. The inflammatory phase constitutes about 10% of healing time.[1-5]

The second, or reparative phase, begins within four to five days of injury, assuming that normal progression of healing occurs. This second phase overlaps with the end stage of the inflammatory phase (phase 1). [1-5] This reparative phase is characterized by the invasion of pluripotential mesenchymal stem cells which differentiate into fibroblasts, chondroblasts and osteoblasts. This diverse population of cells is responsible for the formation of the soft fracture callus and its subsequent transformation to woven bone. Concurrent angiogenesis within the periosteal tissues and marrow space helps to route the appropriate cells to the fracture site. This process contributes to the formation of a bed of granulation tissue. Under optimal conditions, nests of cartilage cells are often apparent in the reparative phase as early as five days after injury together with some early evidence of osteoid production. Thus, the callus begins forming, stabilizing the fracture ends. The process of mineralization is then initiated, which serves to stiffen and strengthen the damaged tissue.

The third phase of bone healing, the remodeling phase, is the longest phase of healing.[1-5] It overlaps significantly with the reparative phase. This stage is characterized by the slow modeling and remodeling of the fracture callus from woven to mature lamellar bone and ultimately the restoration of the bone to normal or near-normal morphology and mechanical strength.

This whole process of complex fracture healing requires that the appropriate cell populations (fibroblasts, macrophages, chondroblasts, osteoblasts, osteoclasts) are recruited at the right time to the correct anatomic site, and that relevant genes (genes controlling matrix production and organization, growth factors, transcription factors) are expressed at the appropriate time, place and amount.[1-5] Considering the complexity of this process, it can be anticipated that some percentage of fractured bone healing will be delayed and may halt altogether, resulting in a condition known as nonunion.

Bones heal at different rates leading to different standards for the time by which healing is expected.[6] In addition, for a given anatomic location, the type of fracture is another factor in

setting the expectation for time to healing. Data from the United States shows that of the six million fractures that occur annually, the healing process of almost 10% is delayed (defined as healing not completed by three months).[2] A significant proportion of these delayed unions will not heal by nine months (characterized as nonunion).

At present, there is no uniformly accepted method in diagnosing fracture nonunion applicable to all fractures given variations in bone tissue and fracture characteristics.[34] Even for fractures in a given bone, there is a range of opinions regarding the time by which a fracture is expected to heal. The term delayed union describes fractures which have not healed within an expected time frame. Once an assessment of delayed union is made, most authors define nonunion as the absence of signs of healing for an additional three months. Further, there are variations in the specific radiographic and clinical criteria used in diagnosing nonunion. A survey study among orthopaedists showed that 79% of surgeons used radiographic evidence of a lack of cortical continuity as their primary means of defining nonunion fracture healing, but that 42% also used weight bearing and 37% also used pain on palpation of the fracture site as diagnostic criteria together with cortical continuity.[34] Clinical characteristics of fracture nonunion include inability to bear weight, pain on palpation of the fracture site, or motion at the site. Despite these imaging and clinical methods, determination of the presence of nonunion can be very difficult and is often dependent on clinical judgment.

Factors associated with the occurrence of delayed union and nonunion have been identified,[7,8,34] including the severity of the fracture, the location of the fracture, the nature of the blood supply to the bone, the extent of soft tissue damage and its interposition, bone loss, air contact and contamination, and whether a tumour is involved. The incidence of delayed or nonunion may increase due to the treatment itself involving inadequate reduction, poor stabilization, distraction, damage to the blood supply, or postoperative infection. Systemic factors have also been identified as contributing to the development of delayed or nonunion. These factors include smoking, alcoholism, age, chronic illness (e.g. diabetes mellitus), malnutrition, and use of medications (e.g. NSAIDs and steroids).

Treatment options for nonunion are designed to enhance the cellular processes that lead to fracture repair. The exact approach depends on the condition of the fracture, surrounding tissue damage, patient's preferences, comorbid conditions, and the physician's preference and experience.[9] Once nonunion has been diagnosed, the presence or absence of infection is a key determinant of treatment.[4,10-12] In general, when infection is felt to be present, implantation of new hardware for stabilization may need to be delayed until after antibiotic therapy and surgical debridement. In some cases, previously implanted hardware needs to be removed. An external stabilization device is sometimes used for stabilization of the fracture site in this setting. Once infection is under control, the fracture site is reassessed for nonunion. The stability of the fracture site may range from none (freely movable bone fragment) to fairly rigid (fragment with good interdigitation and stiff fibrous or cartilaginous tissues across the site).[3] Noninfected nonunions may be divided into those in which lack of stability is felt to be the major problem

and those in which the biological processes necessary for bone formation have failed. In practice, both instability and biologic deficits frequently coexist with one being the dominant issue for initial nonunion treatment.[10-12] The assessment of stability of the fracture site is partially based on the radiographic appearance of the fracture. If nonunion is accompanied by exuberant callus formation, it is generally assumed that the biologic process is intact but that excessive motion or strain at the fracture site has disrupted the healing process. Breakage or loosening of hardware from stress of motion at the fracture site may be seen on x-ray. Motion at the fracture site may be present on clinical examination.[4,10-12] If the acute fracture has been treated with closed reduction and external support (e.g. cast, brace or external fixator), internal fixation may be necessary to achieve alignment and stability of the nonunion site.[10-12] If internal fixation was used in the acute fracture management but stability was not achieved, the hardware may be replaced or stabilization supplemented with either additional internal or external fixation (e.g. replacing an intramedullary nail with one of bigger diameter in tibial or femoral shaft fracture). With the availability of various hardware and techniques to stabilize nonunited fractures, the choice is determined largely by the characteristics of the fracture site, patient preference and the surgeon's experience.[4]

At the other end of the spectrum is nonunion with good alignment and adequate stability but no visible callus and a persistent gap between fracture fragments on the x-ray. In this situation, once again, a defect in the biological process is presumed. Bone resorption can occur at the bone ends and fibrous or fibrocartilaginous tissue may fill the gap, or a synovial capsule may form around bone ends creating a pseudoarthrosis. It was previously assumed that such nonunions, a.k.a. atrophic nonunions, were relatively avascular. However, this assumption may not be true. Reed et al.[13] showed that there was no difference in the number of median vessel counts between hypertrophic and atrophic nonunions. Clinical experience has shown that fresh bone autograft, which contains viable cells and growth factors, will stimulate the healing process in the nonunion site. At present, a bone graft obtained from the patient's iliac crest or from a bone site near the fracture is the most common treatment for failure of the healing process.[4] However, retrieval of an autograft may cause significant morbidity in terms of blood loss, pain, and risk of infection. Bone marrow harvested by aspiration also contains osteogenic cells and has been used in the treatment of nonunion. It can be delivered by percutaneous or open routes to the nonunion site. In this type of treatment, time to union and volume of callus formed relates to the number and concentration of progenitor cells in the aspirate.[14] It should be noted that recent developments with bone morphogenetic protein (BMP-7) or osteogenic protein-1 may well be instrumental in addressing this problem. Allografts, such as from cancellous, cortical or corticocancellous bone, may be employed in this particular situation as well. However, an untreated allograft is highly likely to provoke an immune response that leads to graft rejection (i.e. excessive local inflammation and subsequent resorption). As such, allografts are usually treated by freezing, freeze-drying or irradiation. The efficacy of an allograft depends highly on its processing, handling, and preservation methods.[4] Once again, recent developments with bone morphogenetic protein (BMP-7) or osteogenic protein-1 may well be instrumental in addressing difficulties with bone grafting.

Amputation may also be necessary in treating nonunions, particularly when associated injury to soft tissue and peripheral nerves would leave the limb nonfunctional or persistently painful even with bony union.[4]

Many orthopaedists consider nonunion to be a cessation of the healing process which if left untreated will never heal. Mayr et al.[9] stated that, "…orthopaedics literature is quiet clear in stating that all processes have stopped in a nonunion and healing can only be initiated by another procedure since no spontaneous healing will take place." It should be noted that this perception of nonunion becomes the basis for studies on the effectiveness of ultrasound using patients as their own controls, such as those conducted by Mayr et al.[9] and Nolte et al.[10]

Ultrasound

Ultrasound is an acoustic radiation at frequencies above the limit of human hearing.[17] It is a form of mechanical energy that can be transmitted into the body as high frequency acoustical pressure waves. Ultrasound has many medical applications including diagnostic, operative, and therapeutic procedures.[18] Ultrasound achieves biological results in surgical or therapeutic fields by raising the temperature of the tissue, with intensities ranging from 0.20 to 100 W/cm^2. In contrast, intensities for diagnostic imaging are much lower (0.5 to 50 mW/cm^2) and considered as non-thermal stimuli.[19]

The application of ultrasound on fracture healing was observed in 1950 by the demonstration of enhanced callus formation in a rabbit model by Maintz.[20-22] In 1953, the treatment of 181 delayed and nonunion fractures with ultrasound was reported by Hippe and Uhlman.[22] Eighty-five percent of these delayed and nonunion fractures healed by the use of 800 kHz ultrasound of 1 to 1.5 W/cm^2 for 5 minutes every 2 days with a total of 10 to 12 treatments.[22] It was not until the early 1980s that ultrasound stimulation of bone healing received more attention and more studies involving human subjects were published. In 1983, Xavier and Duarte reported that low intensity ultrasound (30 mW/cm^2) healed 70% of 27 nonunion patients by employing 20 minutes daily of ultrasound exposure on the nonunion site.[23] The first double blind trial of ultrasound, focused on the healing rate of fresh closed or grade 1 open tibial fractures, was reported by Heckman et al. in 1994.[18] Ultrasound based on the frequency used by Xavier and Duarte is the one used in the Exogen® system, the topic of this systematic review.[24]

The Exogen® system (a.k.a. Sonic Accelerated Fracture Healing System, manufactured by Smith and Nephew) consists of a 1.5 MHz sine wave which is administered in a burst of 200 μs, followed by a pause of 800 μs (pulsed 1:4). This is repeated 1000 times per second (repetition rate 1KHz). The average intensity over space and time is 30 mW/cm^2, and the average intensity over the 'on' period is 150 mW/cm^2. The ultrasound is administered for 20 minutes daily through a non-moving transducer.[24] As part of post market surveillance, Exogen maintained a database of the worldwide prescription use of the device in the treatment of fresh fracture,

delayed union, and nonunion. In 2000, it was reported that over 9000 prescriptions of Exogen were issued worldwide, including 5058 fresh fractures, 3173 delayed unions and 1546 nonunions.[22] The heal rate was 94%, 90%, and 83%, respectively.

Regardless of the success rate of low intensity ultrasound in treating fractures, the mechanism of ultrasound in affecting fracture healing or living cells and tissues in general is still unknown.[20,22,25] Thermal effects of ultrasound are not considered to play a role in the ultrasound treatment of bone because the intensities currently used are low (the Exogen system of 30 mw/cm^2 is considered incapable of heating bone), hence non-thermal mechanisms must account for the observed effect in the bone healing process.[20,23] It has been argued that the beneficial effect of ultrasound on bone healing is due to the piezo-electric phenomenon.[20,23] Bone is piezo-electric which means that an electric potential is produced in bone when bone is subjected to mechanical stress. Wolff's law states that bone remodels according to functional demands. It is assumed that the stress-generated potential in bone serves as a signal which controls bone remodeling.[23] The stress-generated potential produced by the ultrasound serves as a surrogate for the regulatory signals that normally arise as a result of functional loading of the skeleton but which are absent following bone injury. However, this theory has been challenged by the fact that the level of stress-potential generated by the ultrasound is small compared to those generated by muscle activities.[22]

Materials and methods

Literature searches, up to March 9, 2006, were undertaken on the Ovid®-based commercial medical literature databases that include Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects, The Cochrane Central Register of Controlled Trials, BIOSIS, CINAHL, EMBASE, MEDLINE® In-Process, Other Non-Indexed Citations, MEDLINE® and MEDLINE® Daily Update. Searches employed a combination of keywords ((fracture$ AND (nonunion$ OR non union$ OR non-union$ OR delayed union)) AND (exogen OR exogen bone healing system OR low intensity ultrasound OR bone stimulator$). The search was limited to human subjects and articles published in the English language from the inception of each respective database to March 9, 2006.

There were 17 published research papers identified from these searches. Of these 17 articles, 13[2,15,16,18-20,23,26-31] were thought to be relevant to the objectives of this review and were retrieved in full.

Through the Evidence-Based Practice Group's regular literature surveillance, prior to the request for this review, we have seen two systematic reviews on the topic of low intensity ultrasound (Exogen® system) for treating bone fracture that were published by health technology assessment organizations in Australia[32] and Canada.[33] Hence, the literature search was expanded to include websites of various technology assessment agencies, including the

International Network of Agencies for Health Technology Assessment, and its member organizations, representing Canada (Quebec Aetmis, Alberta, and the Canadian Agency for Drugs and Technologies in Health (formerly the Canadian Coordinating Office for Health Technology Assessment)), the United States (Veterans' Affairs Technology Assessment, Agency for Healthcare Research and Quality (AHRQ) and ECRI), Australia (Medical Services Advisory Committee, ASERNIP), Sweden (SBU), UK (NICE), and New Zealand. This second search identified one systematic review on the role of bone growth stimulating devices in general in healing nonunion fractures.[34] This third systematic review, published in September 2005, was produced by the ECRI for the AHRQ upon request from the US Medicare Medicaid.

Websites of other WCBs in Canada (including Yukon and the Northwest Territories, Alberta, Saskatchewan, Manitoba, Nova Scotia, Newfoundland, PEI, Quebec, and Ontario) and in the US (Washington State, Colorado, California, and Oregon); private health insurance companies (including Aetna, Blue Cross Blue Shield, Regence, WellMark, Cigna, Humana, Permanente Medical Group, Tuft, and Western Health Advantage); and websites of physical therapy and orthopaedics associations including the US, the UK, Canada, and Australia were also searched in order to investigate the reimbursement status of the Exogen® system in treating fracture nonunion.

Results

Evidence from systematic reviews (Level 1 evidence, Appendix 1)

1. Low intensity ultrasound treatment for acceleration of bone fracture healing – Exogen® bone growth stimulator (November 2001).[31]

   The purpose of this systematic review conducted by Australia's Medical Services Advisory Committee (MSAC) was to investigate the safety and effectiveness of low intensity ultrasound (c.q. Exogen® system) in the treatment of bone fractures. The authors conducted an extensive systematic search, employing various databases including MEDLINE, HealthSTAR, DARE, Cochrane, EMBASE and EconLit from 1966 to October 2000, in order to identify published research on ultrasonic therapy and fracture healing. Further information was also sought from various health technology assessment agencies, evidence-based medicine databases, and references cited in publications previously retrieved. In addition, information was also requested from Smith and Nephew as part of their device approval request. Manual searches were also done among bibliographies and reference lists. The searches were limited to articles published in the English, German, and French languages. Six published papers and three case series were included in this systematic review. Upon examination, these articles were also cited in the most current systematic review published by the AHRQ.[33] Hence, the EBPG decided not to report at length on this systematic review.

The MSAC concluded that:

- The device is relatively safe. However, the device should not be used prior to skeletal maturation or among patients with pacemakers.
- On the basis of evidence available at that time, it was not possible to conclude that low intensity ultrasound was more efficacious than other treatments of fresh fractures (results of the studies were contradictory).
- With regard to the effectiveness of the device in treating fracture nonunion, only case series data was available at that time. These data represented minimally acceptable low level evidence to support the efficacy of the device for treatment of fracture nonunion. It should be noted that this conclusion was restricted to patients with radiologically confirmed fracture nonunions who had failed previous treatment.
- Overall, MSAC did not support the reimbursement of the device for acceleration of bone fracture healing.

2. Low intensity ultrasound (Exogen®) for the treatment of fractures (March 2004).[32]

The Quebec Agency for Health Services and Technology Assessment (AÉTMIS) conducted this systematic review upon request from Quebec's Société de l'assurance automobile du Quebéc. The purpose of this systematic review was to investigate the efficacy and safety of the Exogen® system in fracture healing. A literature search, up to September 2003, was conducted by employing extensive keywords. The search was limited to MEDLINE and the Cochrane library as well as some websites (the author did not specify which websites). The search strategy was not available in the published paper, however, upon request of the EBPG, the author provided the search strategy. The primary studies used in this systematic review were the same as those used in the previous systematic review by the MSAC[31] indicating a paucity of new data on the topic.

The author concluded that:

- From the standpoint of safety, available studies did not report any adverse effects associated with the use of low intensity ultrasound.
- The available efficacy evidence of low intensity ultrasound in the acceleration of fracture healing, prevention of fracture nonunion, and treatment of fracture nonunion is weak. It should be noted that the evidence for the efficacy of low intensity ultrasound in treating fracture nonunion is the same as the evidence assessed by the MSAC[31] above, i.e. the evidence came from large case series (level 4 evidence).

- With regard to the treatment of fracture nonunion, the author suggested that low intensity ultrasound could be employed after failed surgical intervention and after the consolidation process, as measured by multiple view serial radiographs, has ceased for several months. This conclusion was applicable to tibial nonunion fractures. The efficacy of low intensity ultrasound should be assessed individually for other fracture sites in light of the prognosis specific to these fractures and of the clinical context.

In the end, the author concluded that there was insufficient evidence to recommend low intensity ultrasound for the acceleration of fracture healing and the prevention of fracture nonunion. However, due to the grim prognosis of fracture nonunion, the author recommended that it was reasonable to consider the application of this device in treating fracture nonunion. Hence, AETMIS at the time considered low intensity ultrasound as an exceptional treatment option for a very limited number of patients.

3. The role of bone growth stimulating devices and orthobiologics in healing nonunion fractures (September 2005).[33]

   This is a comprehensive, up-to-date systematic review conducted by the ICSI for the AHRQ upon request from US Medicare & Medicaid. The purpose of this review was to answer questions around risk factors for developing nonunion fractures, the diagnosis of nonunion fractures, current standard treatment of nonunion fractures, intermediate and patient-reported outcomes of treatment for nonunion, evidence for variation in outcomes that may be attributable to surgeons, procedures or institutional characteristics, and, most importantly, the evidence for the benefit and harm of bone growth stimulating devices and orthobiologics for the treatment of fracture nonunion.

   By employing various keywords and medical subject headings, the authors comprehensively searched various databases, including the Cochrane library, ECRI, EMBASE, LexisNexis, MEDLINE, HealthSTAR, CancerLit, US Medicare & Medicaid, the US FDA, and the US National Guideline Clearinghouse. It should be noted that some of these databases, particularly various databases from the ECRI, are not available to the EBPG. The search was done up to August 2005. The authors also conducted a manual search including abstracts presented in various orthopaedic associations' proceedings, bibliographies, and references from the articles retrieved. Gray literature was also extensively searched. Studies on adult human subjects, published in the English language, from any type of study design were included in this systematic review. Articles were excluded if they included less than 20 patients, were available as abstracts only, or were multiple articles from the same data source (in this case the most current publication was included). The authors identified 24 primary studies on various bone growth stimulating devices and orthobiologics in treating fracture nonunion, including three on low intensity ultrasound that matched the inclusion and exclusion criteria. Upon examination of the primary studies included in the section of the review on

low intensity ultrasound for treating fracture nonunion, all primary studies used in the two previous systematic reviews,[31,32] as well as the primary studies identified by the search conducted by the EBPG above, were available in this review. It should be noted that there was no new data available on this topic, again suggesting the paucity of research on the topic, particularly in the form of high quality randomized controlled trials.

This review identified three case series using the Exogen® system to treat nonunion in 1446 patients. These case series consistently reported that a high percentage of nonunions healed during ultrasound therapy. While the results of these studies suggest that low level intensity ultrasound promoted the healing of nonunion fractures, these results could not rule out the role of other concurrent treatment procedures, such as stabilization of the nonunion, in contributing to the observed effects. This review did not provide information on the characteristics of fracture nonunion patients who may benefit from concurrent treatment of low intensity ultrasound.

Characteristics of fracture nonunion patients who may benefit from low intensity ultrasound stimulation

A large case series of patients (1317 patients) with delayed and nonunion fractures reported by Mayr et al[14] provided some information on the characteristics of patients with nonunions who may benefit from the application of low intensity ultrasound as an adjunct treatment. The characteristics of the nonunion patients include:

- Nonunion fractures of the scaphoid, radius or radius-ulna, femur, tibia or tibia-fibula and foot (these fractures had > 80% healing rate)
- Patients aged between 31-60 years
- Patients on steroids, NSAIDs, anticoagulants, or calcium channel blockers
- Current smokers
- Patients with comorbid diseases including diabetes mellitus, alcohol/drug use, infections, or osteoporosis

Reimbursement status of low intensity ultrasound for treating fracture nonunion among various insurance companies in the US

In general, the Washington State Department of Labor and Industries[34] and various other private health insurance companies in the US, including US Medicare,[35] Aetna,[36] Cigna,[37] Blue

Cross of California,[38] Wellmark,[39] and Regence[40] provide coverage for the application of low intensity ultrasound as an adjunct treatment of fracture nonunion.

Generally, coverage is provided for long bone nonunion with the exception of the scaphoid. Meanwhile, fracture nonunion of the cranium or vertebrae, and those that are tumour related are excluded from coverage. Coverage also specifies the requirement of a minimum of two sets of radiographs of multiple views obtained prior to starting treatment with the ultrasound, separated by at least 90 days, together with the written interpretation of the physician stating that there has been no clinically significant evidence of fracture healing between the two sets of radiographs. Coverage also requires that at least one surgical intervention for the treatment of the fracture has failed.

These organizations generally do not cover the application of low level ultrasound in treating failed fusions, delayed union, fresh fractures, congenital pseudoarthrosis, fractures involving immature skeletal systems, and nonunion fractures with fracture gaps > 1 cm.

Short summary of the role of other bone stimulating devices and orthobiologics in treating fracture nonunion

This summary is extracted from a high quality systematic review produced by the US ICSI.[33]

- Pulsed electromagnetic field stimulation (PEMF)

  Seven studies, including two randomized controlled trials (RCT), were included in the PEMF review section. These studies involved 403 patients and examined the role of PEMF in treating tibial nonunion. Overall, the results consistently indicated that nonunions heal in patients treated with PEMF, but the effect of PEMF could not be separated from the effect of concomitant fracture site stabilization provided by external fixations such as casts and external fixators.

- Direct current or capacitive coupling

  Four studies, including one RCT on capacitive coupling, were included in the direct current and capacitive coupling review section. These studies involved a total of 351 fracture nonunion patients treated with direct current or capacitive coupling. The majority of these patients had tibial nonunions. Even though these studies consistently demonstrated healing of fracture nonunions during treatment with direct current or capacitive coupling, the effect of these therapies could not be separated from the effect of concomitant immobilization of the fracture sites.

- Extracorporeal shockwave stimulation

Six case series involving 430 fracture nonunion patients were included in the extracorporeal shockwave stimulation review section. Five of these studies were conducted in Europe and one was conducted in Taiwan. These case series reported healing rates between 50% to 80%, however, the effect of shockwave therapy could not be separated from the effect of immobilization in these uncontrolled studies.

- Orthobiologics

  Four studies, involving 214 patients, were included in the orthobiologics review section. One study was an RCT involving the BMP-7 (OP-1®) implant from Stryker Biotech. This RCT showed that the OP-1 implant in conjunction with internal fixation was not inferior to autogenous bone graft in the treatment of tibial nonunion.

  Three other studies were retrospective case series examining AlloMatrix Injectable Putty® (Wright Medical Technology), which contains demineralized bone matrix, carboxymethylcellulose, OsteoSet® ($CaSO_4$), and the use of a composite allograft with partially purified human bone morphogenetic protein (hBMP). The results of these case series were inconclusive due to the nature of the study design itself.

Overall, it can be concluded that PEMF, direct current, capacitive coupling, extracorporeal shock wave therapy, and orthobiologics should not be applied as standalone therapy without adequate immobilization of the fracture site. These treatment methods may work as an adjunct to immobilization of the fracture site.

Summary/Conclusions

- Fracture healing is a complex process involving various factors that need to occur at both a specific time and a specific place.
- Data from the US has shown that during fracture healing, up to 10% can be categorized as delayed unions. A significant proportion of these delayed unions develop into nonunions.
- There is a lack of agreement among the experts with regard to diagnosing fracture nonunion. A majority of the experts employed a combination of clinical signs and radiological evidence in diagnosing fracture nonunion.
- Even though ultrasound has been applied in treating fractures since at least the early 1950s, its role in fracture healing is not well understood.
- To date there is no high level primary research providing evidence on the efficacy/effectiveness of low level ultrasound in treating fracture nonunion.

- Low level evidence (large case series) has shown that low level ultrasound is effective as an adjunct to good immobilization (especially that provided by an external immobilizer) in treating fracture nonunion.
- Low level ultrasound may be effective among patients with long bone or scaphoid fractures, aged between 31-60 years, even those who may have comorbid illnesses, who have been treated with other drugs, or who are current smokers.
- Other adjunct treatments for treating fracture nonunion are also available, including pulsed electromagnetic field stimulation (PEMF), direct current or capacitive coupling, extracorporeal shockwave stimulation, and orthobiologics (especially BMP-7).
- In general, various other insurance companies provide reimbursement for low level ultrasound in treating fracture nonunion of long bones and the scaphoid.

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Appendix 1

WorkSafeBC - Evidence-Based Practice Group Levels of Evidence (adapted from 1,2,3,4)

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic review of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

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