Stimulators of fracture repair

Introduction

A road traffic accident is reported every 3 min and death every 10 min. With increasing burden of trauma; fractures identifying therapeutics for enhancing fracture healing will remain paramount. In United States alone, an estimated 15.3 million fractures receive treatment annually, 5–10% of which are complicated by nonunion or delayed union.[1] Delayed union or nonunion can result in multiple surgeries and cause significant patient morbidity and loss of limb function. Because the current "gold standard", autogenous bone grafting is costly, time-consuming, and itself associated with morbidity, there remains the need for other technologies to enhance healing. This article reviews current available orthobiologic, biophysical method, and pharmacological agent to enhance fracture healing.

Bone grafting and bone graft substitute

Various grafting materials are available to enhance fracture repair. These materials vary widely in composition, mechanism of action, and clinical results.

Autogenous bone grafts are gold standard for treatment of nonunion, but they have several limitations such as donor site complication, delay in ambulation, pain, and increase in hospital stay.

Allografts are attractive alternative to autograft, but carry risk for transmission of disease. Because of the latency period between virus detection and infection (e. g., 22 days for HIV, 70 days for hepatitis C virus, and 56 days for hepatitis B virus), the bone bank must hold the material appropriately before releasing it. The tissue bank must know the source of the material and must thoroughly screen donors.

Demineralized bone matrix (DBM) is a product of processed allograft bone and contains collagen, proteins, and growth factors extracted from the allograft bone. DBM facilitates the natural processes of bone formation by presenting an increased surface area that serves as a site for cell attachment. However, there is some question about the viability and effectiveness of the inductive proteins.

Conductive substrates include the calcium ceramics, that is, calcium phosphate and calcium sulfate. Both families of calcium ceramics are very similar, but differ in crystalline properties, rates of incorporation and osteointegration, handling, and delivery systems. Studies have demonstrated the efficacy of these materials primarily for metaphyseal defects, but caution is advised for solitary use in diaphyseal defects. New data indicate that the calcium ceramics not only may act as conductive agents but also may increase local demineralization and release of bone morphogenic proteins (BMPs).[2]

Platelets degranulate and release a number of factors, including platelet-derived growth factor (PDGF), transforming growth factor-ß (TGF-ß), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF). These factors have direct chemotactic and mitogenic effects on osteoblasts and osteoblast precursors, and act synergistically to help stimulate bone remodeling and healing. Although platelet gel is not a true osteoinductive material, it is "osteopromotive", that is, the factors tend to promote or facilitate bone growth and thus enhance bone healing. Platelet gel appears to function best as a physiologic carrier for other graft materials.

BMPs The BMPs belong to the TGF-ß superfamily of growth and differentiation factors. Unlike DBM, which is a mixture of BMPs and immunogenic noninductive proteins, the pure form of BMP is nonimmunogenic and nonspecies specific. The BMPs are true "osteoinducers". As they are released, they feed back onto circulating undifferentiated perivascular mesenchymal cells (stem cells), changing them directly into osteoprogenitor cells. BMPs are available through recombinant human (rh) gene technology. Those most extensively studied are rh-OP-1 (osteogenic protein 1), also known as rhBMP-7, and rhBMP-2.

Aspirate injection. Bone marrow has been used to stimulate bone formation in skeletal defects and nonunions. The bone marrow can be aspirated from the iliac crest and injected percutaneously, under fluoroscopic guidance, into the nonunion site. The limited clinical data appears to indicate that the use of bone marrow aspirate is a very promising technique. The local iliac harvest and aspirate concentration is very technique-dependent,[3] and failures are usually due to inconsistent aspiration technique.

Biophysical stimulators of fracture healing

Various biophysical methods have been proposed to accelerate healing such as low-intensity pulsed ultrasound (LIPUS), pulsed electromagnetic fields (PEMFs), low-power direct currents (DCs), and extracorporeal shock waves.

LIPUS is a relatively new tool for accelerating fracture healing. It has a frequency of 1.5 MHz, a signal burst width of 200 ms, a signal repetition frequency of 1 kHz, an intensity of 30 mW/cm,[4]

and an administration time of approximately 20 min/day. In 1983, Xavier and Duarte demonstrated the successful application of LIPUS (30 mW/cm2) as a treatment for human nonunions with a 70% healing rate for 26 cases without harmful effects.[5] There are several attractive features of LIPUS.[6] No harmful effects have been reported even in the presence of infection, osteosynthesis, or metallic devices. The conservative nature of the modality may help in avoiding additional operative procedures. Its ease of use for the instructed patient allows for self-administration at home. Basic science[7] and some clinical trials[8,9] have shown that LIPUS could be a useful method for enhancement or acceleration of healing in some kinds of fresh fractures and nonunions.

Electrical Stimulation for Fracture Healing In 1957, Fukada and Yasuda[10] described the "piezoelectric effect of bone", the generation of electrical potentials in response to compression and tension. This pioneering work led to the hypothesis that electrical potentials induced by mechanical force could potentially regulate the process of bone formation. In vivo studies using different animal models of nonunion have suggested that electrical stimulation has the capacity to increase callous volume and increase mechanical strength of healing bone as compared with controls.[11,12]

Electric and electromagnetic fields can be generated and applied to bones affected by delayed union or nonunion through 1 of 4 currently used methods: DC, PEMF, combined magnetic fields (CMFs), or capacitive coupling (CC).[13] Each method is associated with different advantages and disadvantages and has its own specific clinical indications.

DC electrical stimulation involves the surgical implantation of a cathode at the fracture site and an anode in the nearby subcutaneous tissue, with the production of an electric current between them. PEMF therapy is a noninvasive mode of bone growth stimulation involving placement of a wire coil over the fracture site. CC; the electrical field is created by an oscillating electric current produced between two capacitor plates placed on the skin on opposite sides of the fracture. CMFs are produced through the combination of alternating current and DC and produce a constant sinusoidal wave pattern of electric stimulation.

Extracorporeal Shock Wave Therapy

Shock waves are single high-amplitude sound waves generated by electrohydraulic, electromagnetic, or piezoelectric methods that propagate in tissue with a sudden rise from ambient pressure to its maximum pressure at the wave front, followed by lower tensile amplitude.[14] ESWT has been suggested for the treatment of various musculoskeletal disorders such as plantar fasciitis, lateral epicondylitis, calcifying tendinitis, and avascular necrosis of the femoral head. Moreover, ESWT has also been suggested as a stimulator of bone healing, and it has been employed in the treatment of delayed union/nonunion.[15] The exact pathway by which ESWT may exert its effect on bone healing remains the subject of ongoing experimental investigations.

Systemic pharmacological agents for fracture healing

Parathyroid Hormone

Once daily injection of 1–34 PTH increases bone formation on all bone surfaces including trabeculae, endosteal bone, and periosteal bone. Treatment with teriparatide expands osteoblast and osteoblast precursor populations contributing to its bone anabolic effects. Native parathyroid hormone also stimulates expansion of mesenchymal stem cell populations that contribute to osteogenic and chondrogenic cell populations and there is considerable interest into whether teriparatide may have similar stem cell effects. Multiple case reports of healing of fractures of long bones (fresh and nonunion) and of spinal vertebrae have been reported using teriparatide alone with no surgical intervention.[16,17]

Wnt signaling proteins

Wnt signaling is known to be an important pathway during skeletal development, playing a role in chondrogenesis and chondrocyte maturation during bone formation.[18] Wnt signaling appears to be important in the development of osteoblasts from pluripotent mesenchymal stem cells. Several regulators of Wnt signaling have been identified including the secreted proteins, Dickkopf 1 (Dkk1) and sclerostin. Antibodies to both Dkk1 and sclerostin have been developed and appear to have the potential to induce bone formation by allowing Wnt signal transduction.

Conclusion

By 2020; disability from road traffic accident, the major cause of fracture, is predicted to be top cause of disability from disease Although, orthopedic and trauma surgeons are equipped with highly specialized tools to fix fractured bones, even though development of impaired healing is still a great concern. Through the advent of tissue engineering, the ability to repair or regenerate the musculoskeletal system is developing rapidly and expanding in its applications. With the help of quality research in order to enhance the osteogenic potential of cell concentrates, growth factors and osteoinductive substances, would greatly enhance the management of musculoskeletal injuries and diseases in the future.

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References

1. US bone and joint Decade; The burden of musculoskeletal disease in United states. Rosemont, Illinois: American Academy of Orthopedic Surgeons; 2008.
2. Walsh WR, Morberg P, Yu Y, Yang JL, Haggard W, Sheath PC, *et al*. Response of a calcium sulfate bone graft substitute in a confined cancellous defect. Clin Orthop Relat Res 2003:228-36.
3. Muschler GF, Boehm C, Easley K. Aspiration to obtain osteoblast progenitor cells from human bone marrow: The influence of aspiration volume. J Bone Joint Surg Am 1997;79:1699-709.
4. Chao EY, Inoue N, Elias JJ, Aro H. Enhancement of fracture healing by mechanical and surgical intervention. Clin Orthop Relat Res 1998:S163-78.
5. Xavier CA, Duarte LR. Stimulation of bone repair by ultrasound. Rev Brasil Orthop 1983;18:73-80.
6. Strauss E, Ryaby JP, McCabe JM. Treatment of Jones' fractures of the foot with adjunctive use of low-intensity pulsed ultrasound stimulation. J Orthop Trauma 1999;13:310.
7. Pilla AA, Mont MA, Nasser PR, Khan SA, Figueiredo M, Kaufman JJ, *et al*. Non-invasive low-intensity pulsed ultrasound accelerates bone healing in rabbit. J Orthop Trauma 1990;4:246-53.
8. Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF. Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. J Bone Joint Surg Am 1994;76:26-34.
9. Kristiansen TK, Ryaby JP, McCabe J, Frey JJ, Roe LR. Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound. A multicenter, prospective, randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am 1997;79:961-73.
10. Fukada E, Yasuda I. On the piezoelectric effect of bone. J Phys Soc Japan 1957;12:1158-69.
11. Friedenberg ZB, Roberts PG Jr, Didizian NH, Brighton CT. Stimulation of fracture healing by direct current in the rabbit fibula. J Bone Joint Surg Am 1971;53:1400-8.
12. Fredericks DC, Nepola JV, Baker JT, Abbott J, Simon B. Effects of pulsed electro- magnetic fields on bone healing in a rabbit tibial osteotomy model. J Orthop Trauma 2000;14:93-100.
13. Aaron RK, Ciombor DM. Therapeutic effects of electromagnetic fields in the stimulation of connective tissue repair. J Cell Biochem 1993;52:42-6.
14. Gerdesmeyer L, Maier M, Haake M, Schmitz C. Physical-technical principles of extracorporeal shockwave therapy (ESWT). Orthopade 2002;31:610-7.
15. Valchanou VD, Michailov P. High energy shock waves in the treatment of delayed and nonunion of fractures. Int Orthop 1991;15:181-4.
16. Chintamaneni S, Finzel K, Gruber BL. Successful treatment of sternal fracture nonunion with teriparatide. Osteoporos Int 2010;21:1059-63.
17. Oteo-Alvaro A, Moreno E. Atrophic humeral shaft nonunion treated with teriparatide (rh PTH 1-34): A case report. J Shoulder Elbow Surg 2010;19:e22-8.
18. Kawakami Y, Wada N, Nishimatsu SI, Ishikawa T, Noji S, Nohno T. Involvement of Wnt-51a in chodrogenic pattern formation in the chick limb bud. Dev Growth Differ 1999;41:29-40.

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