Journal of Orthopaedic Translation (2017) 9, 60—68

Available online at www.sciencedirect.com

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REVIEW ARTICLE

Pulsed electromagnetic field applications: A corporate perspective

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Received 1 February 2017; received in revised form 24 February 2017; accepted 27 February 2017
Available online 31 March 2017

KEYWORDS
electromagnetic field;
electromagnetic wave;
magnetic field therapies

Summary Corporate establishment of US Food & Drug Administration approved pulsed electromagnetic fields (PEMFs) for clinical applications has been achieved. However, optimization of PEMFs for improvement in efficacy for current indications, in addition to the expansion into new indications, is not trivial. Moving directly into a clinical trial can be costly and carries little guarantee for success, necessitating the need for preclinical studies as supported by this review of the extensive corporate preclinical experience by Orthofix, Inc.

The Translational Potential of this Article: This review illustrates the need to gain enough *in vitro*/*in vivo* knowledge of specific PEMF signals and its target tissue interaction to enable a high success rate in clinical trials.

Introduction and background

Contemporary development of magnetic and electromagnetic field applications as therapeutic modalities started immediately after World War II with designing and manufacturing of various types of electromagnetic signals [1]. During these years, it was established that symmetrical waveforms are less effective than asymmetrical or pulsed signals [2]. These pulsed electromagnetic field (PEMF) signals are inductively coupled to the treatment site and therefore noninvasive [2,3]. The PEMF signals contain a wide range of spectral components allowing for potential coupling to a variety of possible biochemical signalling pathways [4].

The possibility of treatment using electromagnetic fields for various disorders drew corporate interest, in part due to the ability to noninvasively induce an electric current in the target tissue. While electromagnetic studies have included disorders such as major depressive disorder (using transcranial magnetic stimulation) [5], fibromyalgia [6], and osteoarthritis of the knee [7], the only Class III electromagnetic field devices approved by the US Food & Drug Administration (FDA) have been within the category of bone growth simulation/ostegenesis stimulation. Within this category, Orthofix Inc. (Lewisville, TX, USA) originally

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http://dx.doi.org/10.1016/j.jot.2017.02.006

developed three PEMF devices for osteogenesis stimulation: Physio-Stim®, Spinal-Stim® and Cervical-Stim®. Each of these devices incorporates a specific set of triangular shaped PEMF signals (Figure 1). The particular set of signals takes advantage of having its polarization and depolarization within the positive magnetic field range as signals within both the negative and positive part have been found to be less effective [2,8]. While PEMF signals can be varied through alterations of their pulse period, burst period, amplitude, and number of pulses/burst, the specific parameters for the three devices were selected based on preliminary preclinical studies (unpublished data) combined with PEMF field parameter limitations due to engineering considerations such as battery life and device portability.

As mentioned, common for all the approved commercial electromagnetic field devices for osteogenesis stimulation is their classification by the FDA as a Class III device (Table 1). A Class III device requires the establishment of safety and effectiveness of the device through valid scientific evidence before approval by the FDA can be achieved. This is done through the initial FDA approval of an investigational device exemption (IDE) allowing for the device to be used in a clinical study collecting safety and effectiveness data. This data is required to support a premarket approval (PMA) application which upon approval, enables the device to enter the market. This process ensures that safety issues such as hardware failure, inadvertent exposure of incorrect target tissues, incorrect exposure (amplitude, duration etc.), and unanticipated adverse events etc. are considered and evaluated.

The first Orthofix device to receive FDA approval was the Physio-Stim device (Figure 2), which was designed for the treatment of an established nonunion acquired secondary to trauma, excluding vertebrae and all flat bones, where the width of the nonunion defect is less than half the width of the bone to be treated. Note that a nonunion is considered to be established when the fracture site shows no

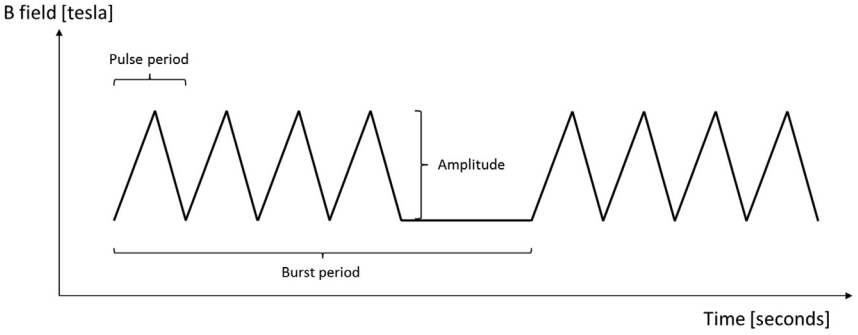

Figure 1 Representation of the Orthofix Pulsed electromagnetic field signal.

Table 1 US Food & Drug Administration (FDA) approved commercial electromagnetic field devices for osteogenesis stimulation.

EMF Device	Manufacturer	Indication	Description
Physio-Stim	Orthofix, Inc.	Treatment of nonunion acquired secondary to trauma, excluding vertebrae and all flat bones	A series of 5 different EMF single coils for various skeletal locations.
Spinal-Stim	Orthofix, Inc.	Adjunct treatment to spinal fusion and as a nonoperative treatment for salvage of failed spinal fusion	Dual coil (coils placed anterior and posterior to spine) acting as a Helmholtz coil at the lumbar spine
Cervical-Stim	Orthofix, Inc.	Adjunct treatment for cervical spine fusion surgery in patients at high risk for nonfusion	Single coil placed posteriorly to the cervical spine
CMF SpinaLogic	DJO, LLC	Adjunctive treatment to primary lumbar spinal fusion surgery for one or two levels	Single coil worn posteriorly at the lumbar spine
CMF OL1000	DJO, LLC	Treatment of nonunion fractures acquired secondary to trauma, excluding all vertebrae and flat bones	A series of 5 different EMF coils (single or dual coil) for various skeletal locations.
EBI Bone Healing System	Zimmer Biomet, Inc.	Treatment of fracture nonunions, failed fusions, and congenital pseudarthrosis in the appendicular system	A series of 12 different EMF single coils for various skeletal locations.

EMF = electromagnetic field.