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Review Article

Electrical stimulation of spinal fusion: a scientific and clinical update

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Abstract

Background context: For over two decades, a number of electrical stimulation devices have achieved increasing acceptance as adjuncts to lumbar spinal fusion. Direct current electrical stimulation, pulsed electromagnetic fields and more recently capacitive coupling have been shown to have varying effectiveness when used to increase the success of lumbar spinal fusion.

Purpose: The various electrical stimulation devices will be reviewed with respect to the available basic science evidence validating their use as spinal fusion adjuncts, as well as a review of the current clinical data available to allow not only a discussion of their overall clinical applicability, but more specifically their use in specific spinal disorders and spinal fusion techniques.

Methods: The existing peer-reviewed scientific literature will be used to ascertain the scientific and clinical efficacy of electrical stimulation to enhance lumbar spinal fusion.

Conclusion: Electrical stimulation devices have emerged as valid adjuncts to attaining a solid lumbar spinal fusion. However, not all stimulators are equally scientifically effective nor are they equally effective clinically in achieving increased fusion success.

Keywords: Electrical stimulation; Direct current; PEMF; CMF; Capacitive coupling; Spine fusion

Introduction

The earliest reported use of electrical stimulation to improve the efficacy of spinal fusion was over a quarter century ago. At that time, Dwyer et al. [1] were the first to show that adjunctive electrical stimulation improved the fusion rate of a diagnostically varied group of patients undergoing both anterior and posterior spinal fusion. Over the next decade, only two additional studies examining the effects of electrical stimulation on spinal fusion were published. Neither of these studies, which were presented at scientific meetings, were ever published beyond their abstract form [2,3]. Both reported improved posterior fusion success using implantable direct current electrical stimulation (DCES).

The paucity of both clinical and scientific studies during the early years of electrical stimulation of spinal fusion resulted in an attitude of skepticism on the part of many spinal surgeons during its first decade of use. However, by 1985, increasing interest in the use of electrical stimulation to improve spinal fusion outcomes resulted in a continually growing number of clinical and basic science studies, which have validated the clinical and scientific utility of electrical stimulation to enhance the success of spinal fusion.

Electrical stimulation devices and proposed mechanisms

Until the recent past, the two types of electrical stimulation used as adjuncts to spinal fusion have been DCES and pulsed electromagnetic fields (PEMF). Direct current electrical stimulation uses an implantable device, which consists of a hermetically sealed generator delivering a constant current of 20 to 40 microamperes to the fusion (depending on the model) through two titanium cathodes connected by insulated wires. This device typically remains functional for a minimum of 6 to 9 months after implantation and may or may not be explanted at the discretion of the surgeon. During a typical posterolateral fusion, after decortication and just before placement of the bone graft material, the cathodes are placed in the lateral gutters touching the transverse processes in order to contact with as much viable bone as possible. Bone graft is then placed about the fusion mass, care being taken to completely span and cover the area of fusion while using the posterior bone graft as insulation

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from any implanted internal fixation devices. Before closing, the generator is placed beneath the dorsal fascia along the paramedian region cephalad to the fusion area, or in the soft tissue proximal to the iliac crest. The generator should be placed in a comfortable tissue pocket so that raising of the skin contour is avoided or minimized. It is important to ensure that the generator (which functions as an anode) is in soft tissue and positioned 8 to 10 cm from the cathodes. The effective area of stimulation surrounding the cathodes is 5 to 8 mm and different geometrical shapes (straight, wave and mesh configuration) allow for maximum contact with the graft material [4,5].

Although the exact mechanism of DCES on osteogenesis is not completely understood, there are a number of physiologic changes that occur. Some of these physiological actions include the attraction of charged proteins and growth factors (electrophoresis), the movement of bone, cartilage and endothelial cells to the fusion site (galvanotaxis), and polarization of cell membranes (voltage gated channels, activation of cyclic AMP triggering a second messenger cascade). Unique to direct current stimulation are specific chemical reactions known as Faradic reactions at the cathode–bone graft interface. The formation of OH and H_2O_2 at the surface of the cathode reduces the local oxygen tension (PO_2) and slightly increases the pH. Reduced PO_2 is noted experimentally in fracture calluses and in newly formed bone, as both growth plate cartilage and bone cells use a predominately anaerobic pathway. Both the electric field effects mentioned above and the Faradic products act both together as well as separately to stimulate calcium uptake [4–7]. A localized increase in pH is known to stimulate osteoblast bone formation and mineralization and inhibit osteoclast bone resorption, so that the rate of new bone formation exceeds bone resorption resulting in a net increase in bone growth [4,8].

In contrast to DCES, PEMF devices are not implantable but are externally worn as one or two coils that generate an electromagnetic field (a time-varying magnetic field producing an induced electric field) across the area of the attempted spinal fusion. These coils are usually worn 3 to 8 hours per day for 3 to 6 months, postoperatively, and are usually incorporated into a brace. The degree of patient compliance with the recommended treatment can hinder the efficacy of these types of devices [9].

The mechanism of action of PEMF in stimulating bone healing is less well understood than DCES. It is hypothesized that only the effects of the induced electric field exert a biological action. Several hypotheses have been proposed, ranging from alterations in cell membrane potentials by the PEMF, to alteration of the molecular configuration of parathormone receptors, to changes resulting in an increase in calcium influx into bone cells [10–12]. Studies by Bassett et al. [13,14] indicate that there is an increase in the calcification of bone-repair–initiated fibrocartilage that may further set the stage for vascularization. Aaron et al. [15] demonstrated increased calcification in a rat model where demineralized bone powder was placed in the subcutaneous tissue of the abdominal flank. This model mimics the bone healing process precisely and showed that the synthesis of cartilage molecules was enhanced by PEMF and subsequent endochondral calcification was stimulated. Yen-Patton et al. [16] demonstrated apparent spontaneous vascularization in vitro with PEMF-stimulated undifferentiated endothelial cells.

Investigations into the molecular biology of electrical stimulation suggest that the electric field may exert a modulating effect on the proliferation and differentiation of target cells and also stimulates matrix and growth factor production. On the other hand, PEMF induce an increase in the levels of bone morphogenic protein (BMP)-2 and BMP-4 mRNA in rat calvarial osteoblasts in comparison to controls [17,18]. This effect was directly related to the duration of PEMF exposure and suggests that clinically applied PEMF have a reproducible osteogenic effect in vitro and simultaneously induce BMP-2 and 4 mRNA transcription. An increase in transforming growth factor (TGF) was shown in atrophic and hypertrophic nonunion cells exposed to PEMF, and in an experiment with M63 cells PEMF demonstrated enhanced osteogenic differentiation in response to TGF [19].

More recently, combined magnetic fields (CMF) and capacitive coupling have been approved for use as an adjunct to improving the success of spinal fusion. Much like the PEMF apparatus, these devices are worn externally and used for up to 9 months after surgery. The CMF device differs from PEMF by superimposing the time-varying magnetic field onto an additional static magnetic field. The device is usually worn for 30 minutes daily. The rationale for the combined field with 30-minute daily treatment was based on animal data, which demonstrated increased bone stiffness at the 30-minute dose. However, the treatment effect was far greater in this animal model with 24-hour per day treatment indicating a dose response [20]. In addition, a comparison of PEMF with CMF in a rabbit tibial osteotomy model showed the two signals to be very similar at equal treatment times [21].

The capacitive coupling device uses small electrodes that are attached to the surface of the skin over the fusion area for constant 24-hour per day treatment. The batteries are changed daily and the electrodes replaced periodically. The true mechanism of action, much like PEMF and DCES, is not completely understood. However, the biochemical pathway by which the osteogenic response is elicited was demonstrated in an ingenious fashion by Lorich et al. [22]. The study design included MC3T3-E1 and rat calvarial bone cells subjected to a capacitively coupled electric field of 20mV/cm. DNA content determined cell proliferation. A process of elimination and detection postulated the biochemical path with known biochemical blocking agents that included verapamil, a calcium channel blocker, W-7, a calmodulin antagonist, indocin, a prostaglandin synthesis inhibitor, bromophenacyl bromide, a phospholipase A_2 inhibitor, and neomycin, an inhibitor of the inositol phosphate cascade. Through observation of cellular proliferation in

electrically stimulated and control samples in the presence or absence of various combinations of these agents, it was hypothesized that the signal transduction pathway mediating the proliferative response of the test cells to the electric field involved transmembrane calcium translocation or movement through voltage-gated (regulated) calcium channels with a subsequent increase in levels of prostaglandin E2 and activation of calmodulin. It was also noted that the inositol phosphate pathway, dominant in mechanically stimulated bone cells, does not play a role in the proliferative response of bone cells to electrical stimulation [23]. If further refinement of this data through repeated experimentation verifies these results, this could be an important point of differentiation between bone healing devices that use electricity versus those that rely on mechanical stimulation (ie, ultrasound). Other studies have clearly shown that capacitive coupling can reverse osteoporosis in a controlled experimental setting. Evidence also exists that shows a change in transforming growth factor beta 1 (TGFβ-1) mRNA in bone cells in response to capacitive coupling [22,24,26].

Scientific and clinical investigations

Before assessing the scientific and clinical efficacy of these spinal fusion adjuncts, it must be appreciated that not all electrical stimulation devices work in the same manner and, similarly, that all spinal fusions do not physiologically or biomechanically heal in the same manner. Obviously, the physiologic and biomechanical forces acting on the healing of anterior interbody and posterolateral fusions are quite different. Anterior interbody fusions are revascularized previously through the vertebral bodies themselves, and the graft material used in the interspace is under compressive biomechanical loading. In a posterolateral fusion revascularization is primarily derived from the surrounding muscle tissue. There is little or no compressive force on the graft material. Thus, the distinct differences between anterior and posterior fusions must be kept in mind when critically weighing the comparative effectiveness of the different types of electrical stimulation devices.

In 1985, the first report of the clinical efficacy of PEMF on spinal fusion was published [27]. This study described the effects of PEMF on established pseudarthrosis in 13 patients who had undergone posterior lumbar interbody fusion. Without additional reparative surgery, 77% of the patients were found to have healed their interbody pseudarthrosis.

Three years later, Kane [28] was the first to publish a large, multicenter series of patients undergoing posterior spinal fusion for a variety of spinal disorders augmented by DCES. This publication actually reported the results of three independent clinical studies. The first study reported the results of 82 patients undergoing posterior spinal fusion with DCES compared with a historical control group of 150 patients fused without DCES. The DCES group was found to have a statistically higher success rate of 91% compared with 81% in the nonstimulated control group, despite the fact that the DCES group had a significantly higher incidence of pseudarthrosis revision. The second was a randomized prospective controlled study in a specifically defined "difficult to fuse" spine fusion population consisting of 1) one or more previous fusion attempts, 2) multilevel procedures, 3) Grade II or worse spondylolisthesis and 4) other risk factors consisting of obese patients, smokers, diabetics and so forth. This randomized study compared 28 patients undergoing posterior spinal fusion without stimulation and 31 patients with DCES. The stimulated group was found to have a successful fusion rate of 81% compared with 54% in the nonstimulated group ($p=.026$). The third study examined 116 patients in an uncontrolled trial of posterior spinal fusion with DCES in the same "difficult" population. The overall fusion rate was 93%.

In 1990, Mooney published the first large multicenter series of patients treated with adjunctive PEMF [9]. Unlike Kane's multicenter studies of DCES used to enhance posterior spinal fusion, Mooney reported on the results of 195 patients undergoing primary posterior or anterior lumbar interbody fusions. None of the patients underwent posterolateral spinal fusion. Overall the fusion rate of 92% was similar to Kane's overall results, but the radiographic criteria for fusion required only 50% incorporation of the graft. Subsequent product labeling indicates that 4-year follow-up of these patients revealed that longer-term success rates had decreased by approximately 24%.

Just before Mooney's publication, in 1988, Lee [29] reported the results of patients treated for posterior pseudarthrosis with adjunctive PEMF. The 67% success rate was not as high as the previously reported success rate of 77% by Simmons [27] in the group of patients treated for anterior interbody pseudarthrosis. In the same year, Simmons published an abstract that reported the first use of PEMF as an adjunct to primary posterolateral spinal fusion [30]. The fusion success rate of 71% was significantly less than that found in those patients undergoing primary posterolateral fusion in Kane's series, and also slightly less than the long-term results of Mooney's patients undergoing PEMF-stimulated anterior and posterior lumbar interbody fusions.

Two other studies examining the use of PEMF on posterolateral spinal fusion have been reported. The first, by Savini et al. [31], involving an uncontrolled study of only 15 patients, and the second, a controlled study of 35 patients by Mammi et al. [32], demonstrated encouraging preliminary results, but longer follow-up evaluations of these patients have not since been reported. The latest clinical study examining the use of adjunctive CMF to enhance noninstrumented posterolateral spinal fusion was reported at the American Academy of Orthopedic Surgeons 2000 meeting. The series revealed an overall success rate of 64% in the stimulated group compared with 43% in the control group [33]. In this clinical trial CMF appeared to be effective only in women with no improvement in fusion rates among men.

There are no other published scientific studies documenting the clinical efficacy of CMF.

Over the last 5 years, a number of additional clinical studies specifically designed to assess the efficacy of DCES on lumbar spinal fusion have been published. In 1996 Meril [34] reported the results of patients undergoing anterior and posterior lumbar interbody fusion with and without DCES. Overall, successful fusion rates were found to be 95% in the DCES-stimulated group compared with 75% in the nonstimulated group. DCES-stimulated patients had higher success rates in all patient subgroups. Particularly interesting was the success rate among patients who were smokers (93%) compared with the success rate of nonstimulated patients (71%) who were smokers.

The remaining studies have focused on the results of DCES-stimulated posterolateral fusions. One study in 1996 reported a success rate of 96% in patients undergoing posterior spinal fusion with pedicle screw instrumentation and adjunctive DCES as opposed to an 85% success rate in those patients fused with pedicle screw instrumentation alone [35]. A similar study in 1999 examining the adjunctive use of DCES in patients undergoing posterior spinal fusion with pedicle screw instrumentation found a success rate in the stimulated group of 95% compared with 87% in the nonstimulated group. In this study DCES postoperative smokers fared much better than smokers without DCES (83% vs. 66%, respectively). Fusions augmented with DCES had a statistically significant increase in the clinical success and significantly higher fusion grades as defined by Dawson et al. [36]. Thus, both radiographically and clinically there appears to be significant benefit for the concomitant use of both DCES and instrumentation. A 1996 prospective study of 118 patients undergoing multilevel posterior spinal fusion without pedicle screw instrumentation stimulated with DCES found success rates to vary between 91% and 93% with a median 5-year follow-up (range, 2 to 10 years) [37].

Despite recent efforts by the health insurance industry to control costs involved in spinal surgical procedures, there have been few attempts to justify the cost effectiveness of these adjunctive electrical stimulation devices. One study in 1996 examined a large database of patients (epidemiological surveillance) and the costs incurred in caring for patients over a 2-year follow-up after being discharged from the hospital after a posterolateral spinal fusion performed with and without pedicle screw instrumentation and with and without DCES [38]. Those patients having a fusion with and without pedicle screw instrumentation but augmented with DCES showed significant long-term cost savings over those patients fused without adjunctive DCES.

The concept of using capacitively coupled electrical stimulation as an adjunct to lumbar spine fusion is relatively new. One study has been published to date [39]. Although commercially available since the early 1990s for fracture nonunions, efficacy in spinal fusion was only recently demonstrated in a multicenter randomized double-blind study. The overall success rate of the stimulated patients (84%) compared with the nonstimulated patients (64%) was statistically significant. Of the groups used to stratify the data, four of seven showed statistical significance between the actively stimulated patients and the placebo patients.

Since the introduction of electrical stimulation as an adjunct to spinal fusion, there have been relatively few studies published examining the effects of electrical stimulation on spinal fusion in carefully controlled experimental settings. The first controlled experimental clinical study, published in 1984, showed no long-term benefit in attaining posterior spinal fusion in canines with postoperative PEMF despite an encouraging but inconclusive early accelerated healing response [40]. However, in 1990 a controlled animal study examining the use of DCES in swine posterior spinal fusions showed for the first time experimentally a statistically significant higher fusion rate in those animals with DCES [41]. In 1989 a posterior fusion study in canines affirmed these positive results when posterior spinal fusions were augmented with DCES [42].

In 1994, a second attempt at increasing the rate of experimentally controlled canine posterior fusion with the use of PEMF likewise failed. This study, substituting a fresh fracture-healing PEMF for the previously used bone-healing PEMF, similarly failed to show any evidence of an enhanced fusion success rate [43]. Another study, which examined the use of PEMF to increase the fusion rate in a rabbit lateral fusion model, failed to show statistically significant fusion success despite an increase in fusion stiffness [44]. Also in 1997, another study examined the effect of PEMF on instrumented posterolateral fusion in beagles. The study revealed a 17% change in bone mineral density of the vertebral bodies in the animals fused with instrumentation but did not show a statistically significant improvement in bone density while treated with PEMF [45].

Recent innovative studies attempting to expand the current use of DCES have led to promising results. One study reported the effects of DCES on improving the fusion success of coralline hydroxyapatite bone substitute in a posterior fusion model in rabbits. The coralline hydroxyapatite fusion stimulated with a high-current direct-current stimulator not only showed improved fusion success over autologous controls, but also showed improved mechanical stiffness [46]. Another study examined the effects of increasing the current density delivered by means of DCES to the posterior canine fusion mass. Higher current densities resulted in statistically significant evidence of increased speed to fusion [25]. A more recent controlled experimental study further expanded the potential use of electrical stimulation. The addition of DCES in sheep undergoing anterior interbody fusion with a titanium cage showed a statistically significant dose-dependent increase in the speed and extent of fusion based on histological, radiographic and biomechanical analysis [47].

Although these attempts to expand on the use of DCES are limited to just a few animal studies, it is apparent that the ultimate potential, at least for DCES, has not been realized.

Conclusions

Over the last quarter century, electrical stimulation has clearly distinguished itself as a clinically beneficial adjunct to improving the success rate of spinal fusion surgery. However, not all adjunctive electrical stimulation is equally effective in promoting successful spinal fusion. Both the current clinical and basic science data establishes direct current electrical as superior to PEMF particularly when used to enhance posterior spinal fusions. Early data on the use of capacitive coupling also shows clinical superiority over PEMF, but not as statistically beneficial as DCES as an adjunct to posterior spinal fusion. As we continue to explore the use of electrical stimulation and its potential influence on other as yet unstudied aspects of spinal surgery, the impact of electrical stimulation as an adjunct to spinal fusion will most certainly grow over time.

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