Electrical Stimulation and Spinal Fusion

a report by
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The earliest reported use of electrical stimulation to improve the efficacy of spinal fusion was over a quarter of a century ago. At that time, Dwyer et al. 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.[1] 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 utilizing implantable direct current electrical stimulation. 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 that have validated the clinical and scientific utility of electrical stimulation to enhance the success of spinal fusion.

Direct Current Electrical Stimulation

Direct current (DC) electrical stimulation utilizes an implantable device, which consists of an hermetically sealed generator delivering a constant DC to the fusion through titanium cathodes connected by insulated wires. This device typically remains functional for a minimum of six to nine months post-implantation and may or may not be explanted at the discretion of the surgeon. The effective area of stimulation surrounding the cathodes is 5–8mm and different geometrical shapes (straight, wave, and mesh configuration) allow for maximum contact with the graft material.[4,5]

Mechanism of Action

The mechanism of action of DC stimulation has been shown to involve the upregulation of a number of osteoinductive factors that are normal physiological regulators of bone formation.[6] These results were observed using a rabbit posterolateral inter-transverse process fusion model that has been found to closely mimic the surgical procedure performed in humans (inter-transverse process arthrodesis) with similar non-union outcome rate.[7] Using this rabbit spinal fusion model, Fredericks et al. investigated the effect of DC stimulation on the expression of factors related to bone healing. An L4–L5 fusion with autograft was carried out bilaterally on rabbits and treated either with or without DC stimulation. The results showed that DC stimulation upregulates the specific temporal and spatial gene expression of osteoinductive growth factors bone morphogenetic protein (BMP)-2, -6, and -7, and it does so by enhancing the normal physiological expressions of these factors. Morone et al. have pointed out the importance of the upregulation of various growth factors at a specific time and location to attain successful fusion, and that each BMP has its own functions and is not interchangeable.[8] The results with DC stimulation support this observation.

Inductive Coupling

In contrast to the DC electrical stimulation (DCES), pulsed electromagnetic field (PEMF) devices are not implantable, but are worn externally 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. The degree of patient compliance with the recommended treatment can hinder the efficacy of these types of devices.[9] The controlled magnetic field (CMF) device differs from that of the PEMF device in that it is made up of a time-varying magnetic field superimposed on a static magnetic field.

Mechanism of Action

Most studies looking into the mechanism of action of inductive coupling technology have been carried out with the PEMF signal using fracture-healing models; only a few studies have been conducted with CMF. Nevertheless, for both types of signals, studies indicate the important role of growth factors in mediating the effects of inductive coupling stimulation on bone healing. CMF stimulation has been found to increase insulin-like growth factor (IGF)-II in rat fracture callus, and the IGF-II levels and receptors in human osteosarcoma-derived osteoblast-like cells.[10-12]

In contrast, Aaron et al. demonstrated the enhancement of transforming growth factor (TGF)-β1 mRNA and protein levels by PEMF coincident with accelerated chondrogenesis using a rat ossicle model.[13]

BMP-2 and -4 mRNA levels have also been found to be upregulated by PEMF in rat calvarial osteoblasts.[14] Brighton et al. investigated the biochemical pathway mediating the effects of PEMF and CMF on bone cell proliferation using mouse osteoblast-like cell cultures.[15] The results showed that the pathway involves the release of calcium ions from intracellular stores, an increase of the cytosolic calcium concentration, and activation of calmodulin, which leads to enhanced bone cell proliferation. A dose response was also observed in this study when the cells were treated with PEMF or CMF for no minutes, 30 minutes, two hours, six hours, and 24 hours. Though there were no significant differences between the PEMF and CMF groups, cell proliferation increased with increasing stimulation time for both PEMF- and CMF-treated groups. A

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dose response effect for both PEMF and CMF was similarly observed in *in vivo* studies using rabbit osteotomy/ ostectomy models.[16,17]

Capacitive Coupling

Unlike PEMF and CMF, the capacitive coupling (CC) device consists of electrodes with conductive gel that are connected to an alternating current (AC) signal generator. The electrodes are placed adjacent to the spine on the skin and produce an electric field at the fusion site.

Mechanism of Action

The upregulation of osteopromotive factors has been found to mediate the positive effects of CC on spinal fusions. Using the same rabbit posterolateral spinal fusion model as described by Boden et al., Fredericks et al. investigated the effects of CC on the expression of bone-related factors on spinal fusions.[7,18] The results showed that CC stimulation upregulates specific temporal and spatial gene expressions of growth factors BMP-2, -4, -6, and -7, TGF-β1, fibroblast growth factor (FGF)-2 and vascular endothelial growth factor (VEGF). In addition, similar to DC stimulation, it was found that CC upregulates these factors by enhancing the normal physiological expressions of the growth factors. The biochemical pathway mediating the response of bone cells to CC stimulation has also been found to involve the calcium signal transduction pathway.[19]

A dose response was similarly observed with this technology. CC stimulation of osteoblast-like cells showed increased cell proliferation with increasing treatment time.[15] Compared with the dose response of PEMF and CMF technologies, CC stimulation resulted in greater enhancement of cell proliferation.

Scientific Studies

Direct Current Stimulation

Nerubay et al. showed an increased rate of posterior fusion success using a swine model.[20] Kahanovitz et al. similarly reported the effectiveness of DC in enhancing fusion success in a canine posterior facet fusion model.[21] All DC-treated animals achieved solid fusions compared with none in the control group.

Other studies have also found that DC stimulation enhances fusion success in a dose-dependent manner. Using a rabbit posterolateral spinal fusion model with autograft, France et al. observed that DC stimulation with 60μA current was superior to that of 20μA stimulation and control unstimulated groups.[22] In a similar model, but in combination with coralline hydroxyapatite bone substitute, Bozic et al. showed that 100μA DC stimulation with bone substitute was significantly better than autograft alone. Toth et al., using a sheep interbody fusion model with an electrified titanium cage, showed 100% fusion rate with 100μA DC stimulation compared with 27% in the unstimulated group.[24] Furthermore, using a canine facet fusion model, Dejardin et al. found that increasing the current density of DC stimulation increased the speed of fusion.[25] The results of these experiments indicate that DC stimulation enhances fusion success in a dose-dependent fashion.

Inductive Coupling

The first controlled experimental spinal fusion study with PEMF was carried out using a canine posterior spinal fusion model.[26] The results showed no statistically significant difference in fusion rates between the PEMF stimulated and unstimulated groups despite observations of a possible early accelerated healing response. Another canine posterior spinal fusion study, using a different PEMF signal, again showed no enhancement of fusion success rates with PEMF.[27]

A histological posterior fusion study with rats indicated enhanced bone callus formation with PEMF initially, but the observed histological pattern became similar to that of controls after eight weeks.[28] Ito et al. investigated the effects of PEMF on instrumentation-assisted posterolateral fusion using beagles.[29] The results showed an increase in bone mineral density of the vertebral bodies of animals with instrumented fusions, but no statistical difference with PEMF treatment.

Capacitive Coupling

Various CC fields and treatment durations were tested using a castration-induced osteoporotic rat model with the electrodes placed adjacent to the paraspinal muscles at the T11 and L4 levels.[30] The results showed that the 60kHz, 100μA signal, the lowest μA signal tested in this study, worked best by significantly reversing the castration-induced osteoporosis and restoring bone mass/unit volume.

Clinical Studies

In 1985, the first report of the clinical efficacy of PEMF on spinal fusion was published.[31] This study described its effects 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 was the first to publish a large, multicenter series of patients undergoing posterior spinal fusion for a variety of spinal disorders augmented by DCES.[32] 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 an 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 non-stimulated control group, despite the fact that the DCES group had a significantly greater number of pseudarthrosis revisions. The second was a randomized, prospective, controlled study in a specifically defined 'difficult to fuse' spine fusion population consisting of:

- one or more previous fusion attempts;
- multilevel procedures;
- grade II or worse spondylolisthesis; and
- other risk factors, consisting of obese patients, smokers, diabetics, etc.

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 non-stimulated group (p=0.026). 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 radiographical criteria for fusion required only 50% incorporation of the graft. Subsequent product labeling indicates that four-year follow-up of these patients revealed that longer-term success rates had decreased by approximately 24%.

Just prior to Mooney's publication, in 1989, Lee reported the results of patients treated for posterior pseudarthrosis with adjunctive PEMF.[33] The 67% success rate was not as high as the previously reported success rate of 77% by Simmons 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.[34] The fusion success rate of 71% was significantly less than 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.

Only one clinical study examining the use of adjunctive CMF to enhance non-instrumented posterolateral spinal fusion has been reported. The series revealed an overall success rate of 64% in the stimulated group compared with 43% in the control group.[35] In this clinical trial CMF appeared to be effective only in women, with no improvement in fusion rates among men.

Over the last decade, a number of additional clinical studies specifically designed to assess the efficacy of DCES on lumbar spinal fusion have been published. In 1996, Meril reported the results of patients undergoing anterior and posterior lumbar interbody fusion with and without DCES.[36] Overall, successful fusion rates were found to be 95% in the DCES-stimulated group compared with 75% in the non-stimulated 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 non-stimulated 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.[37] 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 non-stimulated group. In this study DCES post-operative smokers fared much better than smokers without DCES (83 versus 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.[38] Thus, both radiographically and clinically, there appears to be significant benefit with 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 five-year follow-up (range 2–10 years).[39]

The concept of using capacitively coupled electrical stimulation as an adjunct to lumbar spine fusion is not as well studied as DCES or PEMF. The largest and most comprehensive study examining the use of CC as an adjunct to spinal fusion is a multicenter, randomized, double-blind study.[40] The overall success rate of the stimulated patients (84%) compared with the non-stimulated patients (64%) was statistically significant when combining both radiographic and clinical outcomes.

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 two-year follow-up after being discharged from the hospital following a posterolateral spinal fusion performed with and without pedicle screw instrumentation and with and without DCES.[41] Those patients having a fusion with and without pedicle screw instrumentation, but augmented with direct current electrical stimulation showed significant long term cost savings over those patients fused without adjunctive direct current electrical stimulation.

Conclusion

Over the last 25 years, 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 clinical and basic science data establish DCES as superior to PEMF, particularly when used to enhance posterior spinal fusions. Data on the use of capacitive coupling also show clinical superiority over PEMF. 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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