Direct Current and Capacitive Coupling Electrical Stimulation Upregulates Osteopromotive Factors for Spinal Fusions

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INTRODUCTION

Poor fusion rates in spine surgery continue to pose a challenge to spine surgeons. Nonunions are more common in patients with previously failed fusions, multiple-level fusions, and smoking. Consequently, treatment modalities such as electrical stimulation and spinal instrumentation systems have been designed for use as adjuncts to spinal fusion surgeries to increase fusion success rates. Two forms of electrical stimulation are direct current (DC) and capacitive coupling (CC) stimulation.

The implantable DC-stimulation technology consists of cathodes connected to a power supply which also serves as an anode. The device is surgically implanted with the cathode placed at the fusion site and the anode in the soft tissue. The power supply delivers a constant current of 20, 40 or 60 μA through the cathodes to the fusion site. In contrast, capacitive coupling (CC) stimulation technology is a non-invasive method of generating electric fields in tissues. The device consists of two electrodes with conductive gel that are connected to an alternating current signal generator. The electrodes are placed on the skin over the fusion site.

Clinical studies have shown that both treatments significantly increase fusion success rates, particularly in "difficult to fuse" patient populations. Kane published the results of a randomized, prospective, controlled clinical study on the use of DC stimulation on high-risk patients undergoing posterior spinal fusions.[1] The patient population consisted of those with previous failed fusions, patients with grade II or worse spondylolisthesis, patients requiring multiple level fusions and patients with other risk factors such as obesity, smoking and diabetes. The DC-stimulated group had an 81% overall fusion success rate compared to 54% in the control group. Meril reported the results of patients undergoing anterior and posterior lumbar interbody fusions with allograft.[2] The overall fusion success rate of the DC-stimulated group was found to be 95%, compared to 75% in the control group. In a subset of patients who were smokers, the stimulated group had a 92% success rate versus a 71% in the non-stimulated group. Cases without internal fixation had a 91% success rate in the stimulated group compared to 65% in the control group. For capacitive coupling, Goodwin et al. carried out a randomized double-blind prospective clinical study on the use of CC stimulation as an adjunct to spinal fusions.[3] The overall fusion success rates were found to be 85% for the CC-stimulated group versus 65% for the control group.

Although electrical stimulation has been used for decades to promote bone healing, the mechanisms of action in support of the technologies had not been elucidated. This article describes a study using a rabbit posterolateral spinal fusion model to investigate the role of growth factors in mediating the positive effects of DC and CC stimulation on spinal fusion.[4, 5]

MATERIALS AND METHODS

A single level, posterolateral, intertransverse process fusion, as described by Morone *et al.*[6], was performed on rabbits, bilaterally at L4-L5, with autograft. The rabbits were treated either with DC (SpF®, EBI LP), CC (SpinalPak®, EBI LP) or inactive devices (controls). Animals were euthanized at 3, 7, 14, 21 and 28 days post-surgery. Several regions within the fusion mass were analyzed using Real-Time RT-PCR for mRNA levels of various factors. The results were normalized to β-actin and expressed as fold increase over mRNA levels at time zero.

RESULTS AND DISCUSSION

The mRNA levels of bone morphogenetic proteins BMP-2, BMP-6, BMP-7 and the BMP receptor ALK2 were significantly higher in the DC-stimulated group compared to the control group. In contrast, the CC-stimulated group showed significantly higher mRNA levels of BMP-2, BMP-4, BMP-6, BMP-7, transforming growth factor-β_1 (TGF-β_1), fibroblast growth factor–2 (FGF-2) and vascular endothelial growth factor (VEGF) compared to the control group. In addition, the growth factor mRNAs were expressed in a similar time course in the stimulated and control groups for both DC and CC stimulation. However, sustained elevation of gene expression was observed in the stimulation groups. Figures 1 and 2 are representative plots of the time courses of gene expression for BMP-7 and BMP-2 for DC and CC stimulation respectively. These results show that DC and CC stimulate an osteobiologic response

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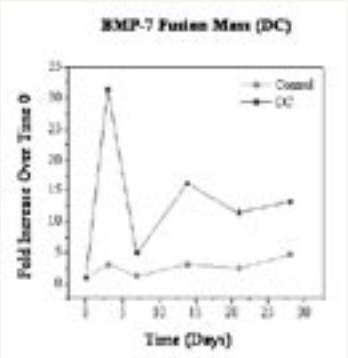

Figure 1:
Plot of the time course of BMP-7 gene expression for DC electrical stimulation.

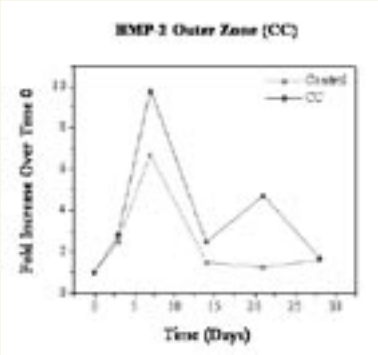

Figure 2:
Plot of the time course of BMP-2 gene expression for CC electrical stimulation.

by upregulating a cascade of growth factors throughout the stimulation time, and they do so by enhancing the normal physiological expressions of most of these factors. DC electrical stimulation upregulates BMP-2, BMP-6, BMP-7 and BMP receptor ALK2. CC electrical stimulation upregulates BMP-2, BMP-4, BMP-6, BMP-7, TGF-β_1, FGF-2 and VEGF.

Another explanation for the mechanism of bone growth secondary to DC stimulation is the result of electrochemical reactions that occur at the cathode which lower local oxygen concentration and increase pH.[7] The primary faradic reaction is $O_2 + 2H_2O + 4e^- \rightarrow 4OH$. The decrease in oxygen concentration enhances osteoblastic activity while an increase in pH increases osteoblastic activity and decreases osteoclastic activity. In addition, the hydrogen peroxide stimulates macrophages to release VEGF, an angiogenic factor that is crucial for bone healing.[8] Regarding CC stimulation, bone formation is promoted through the biochemical pathway involving transmembrane calcium translocation via voltage-gated calcium channels, subsequent activation of calmodulin and increase in prostaglandin E_2 (PGE_2) and TGF-β_1.[9,10]

Using the same rabbit posterolateral spinal fusion model, Morone et. al. has shown that successful spine fusions require precise spatial and temporal expression of a number of growth factors, and that each BMP has its own function and is not interchangeable.[6] At this time, to achieve the desired clinical outcome of a successful fusion using a single growth factor, extraordinary supra-physiologic doses are required. Carrier matrices are currently being developed to improve the local maintenance of the growth factor applied. It has been shown that 92% of active rhBMP-2 in the InFuse device (Medtronic, Minneapolis, MN) is depleted within the first two weeks of implantation.[11] Ectopic bone formation, bone resorption, and antibody formation against rhBMP-2 and rhBMP-7 have also been reported.[12-17] DC and CC electrical stimulation technologies do not have these disadvantages because they upregulate a number of growth factors throughout the treatment time, and they do so by enhancing the normal physiological expression of the growth factors.

SUMMARY

Direct current and capacitive coupling electrical stimulation are indicated as spinal fusion adjuncts to increase the probability of fusion success. Direct current stimulation technology is an implantable device that delivers continuous treatment to the fusion site, and thus is particularly suitable for non-compliant patients. Capacitive coupling stimulation technology is a non-invasive method of generating electric fields in tissues. Both technologies stimulate an osteobiologic response by upregulating a cascade of factors throughout the stimulation time including BMPs and other osteopromotive factors that modulate bone healing, and they do so by enhancing the normal physiological expressions of most of these factors.

The mechanism of action of direct current electrical stimulation involves the upregulation of osteoinductive growth factors BMP-2, BMP-6, BMP-7 as well as the BMP receptor ALK2. Hydrogen peroxide, a faradic product produced at the cathode, also stimulates macrophages to release VEGF. In addition, electrochemical reactions at the cathode lower oxygen concentration and increase pH, resulting in enhanced osteoblastic activity and decreased osteoclastic activity. The net effect is increased bone formation.

Capacitive coupling electrical stimulation enhances fusion success rates by upregulating osteopromotive factors BMP-2, BMP-4, BMP-6, BMP-7, TGF-β_1, FGF-2, VEGF and PGE_2. The mechanism of action of capacitive coupling stimulation also involves transmembrane calcium translocation via voltage-gated calcium channels and subsequent activation of calmodulin.

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