Synergistic Effect of Using a Transcutaneous Electrical Joint Stimulator and an Unloading Brace in Treating Osteoarthritis of the Knee

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Abstract
Medical treatments and less invasive surgical approaches for knee osteoarthritis are variably effective, and total knee arthroplasty (TKA) is generally reserved for the most severe cases. The care gap between more conservative treatments and TKA leaves many patients with unresolv ed pain and loss of function for long periods.

We conducted a study to determine if incorporating the BioniCare stimulator into an unloading brace would produce more rapid improvement and result in increased adherence and efficacy. Two hundred eighty-nine patients treated only with BioniCare served as historical controls and were compared with 225 patients treated with BioniCare combined with an unloading brace.

Means and standard deviations of the changes in scores for pain intensity in the past 48 hours, pain and associated symptoms, patient global assessment, pain on going up or down stairs, and pain on walking on a flat surface and the effect sizes at 1, 3, 6, and 12 months, as well as the percentages of patients achieving at least 20% improvement, and at least 50% improvement, demonstrated that treatment with stimulator and unloading brace combined was significantly superior to treatment with the stimulator alone.

In the United States, more than 20 million people have osteoarthritis (OA) of the knee, and the incidence is increasing as the population ages and becomes more obese. OA is caused by excessive catabolism and inadequate repair of the articular cartilage in diarthrodial joints. Cartilage degeneration in OA begins with matrix architecture disruption, which leads to loss of tissue resiliency. Proinflammatory and inflammatory cytokines activate proteases and collagenases that degrade the cartilage matrix and disrupt chondrocyte function.

Conventional nonoperative treatments for knee OA are education, weight loss, exercise, use of analgesics, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and bracing. Minimally invasive techniques, including intra-articular corticosteroid use and, more recently, viscosupplementation, are used when more conservative therapy is inadequate. Changes in the pharmaceutical treatment of knee OA have not provided major therapeutic advances over the past 5 decades. Furthermore, symptomatic treatment with available NSAIDs, hyaluronans, and narcotics is inadequate in many patients because of lack of efficacy or side effects.

Unloading braces are used to decrease pain and improve function. In most patients, OA affects the medial compartment earlier and more than the lateral compartment. If severe, the OA will cause a varus alignment such that the mechanical axis and the load bearing will pass through the medial compartment. Malalignment increases the risk for progression of knee OA and predicts decline in physical function. Prospective, randomized, multicenter clinical trials have demonstrated the efficacy of unloading braces in the treatment of knee OA over the efficacy of a neoprene sleeve or medical treatment alone.

The therapeutic potential of a transcutaneous electrical joint stimulator (BioniCare; VQ OrthoCare, Irvine, California) is supported by decades of research demonstrating that cartilage formation and repair are stimulated by intrinsic electrical signals generated in the matrix by mechanical compression. Two investigators independently confirmed that the charged proteoglycans of the extracellular matrix together with ionized interstitial fluid act as an electrical field signal transducer when cartilage is deformed in simulated...
Application of the stimulator’s signal was initially determined by electrical probe measurements in rabbits.\(^9\)\(^,\)\(^10\) Farr and colleagues\(^{14}\) reported on a long-term trial of patients with knee OA treated with the stimulator. They found a clear dose–response relationship, with patients reporting significant relief of pain and improvement in function in excess of those reported for NSAIDs, analgesics, and hyaluronans within the first 750 hours of therapy. However, even better outcomes were found in patients who used the device for more than 1750 hours. These outcomes contrast with those of unloading braces, which provide early benefit but are less likely tolerated over time.

VQ OrthoCare developed an unloading brace (OActive, Irvine, California) to be used with its stimulator to obtain the modalities’ complimentary benefits. It was thought that the added effects of the brace would allow more patients to obtain the full 6 to 9 months of stimulator treatment that most patients require for full benefit.

We conducted a study to determine if incorporating the stimulator into the unloading brace would produce more rapid improvement and result in increased adherence and efficacy.

**Materials and Methods**

This study group consisted of 225 patients with knee OA treated at 16 orthopedic and rheumatology practices in the United States between January 2010 and December 2012, and the control group consisted of 289 patients with knee OA treated at 57 orthopedic and rheumatology practices in the United States between September 2003 and July 2005. Study patients were maintained on best medical therapy in addition to stimulator–brace combination treatment, and control patients were maintained on best medical therapy in addition to stimulator treatment in a neoprene sleeve.\(^{14}\)

For both groups, best medical therapy included weight loss, knee-strengthening exercises, NSAID use (if not contraindicated), and/or use of analgesics as tolerated. Corticosteroid injections and viscosupplementation were not allowed during the study trial; orthopedic bracing, corticosteroid injections, and viscosupplementation were not allowed during the control trial.

In both studies, there was no advertising for patients, and all patients signed an informed consent form approved by a central institutional review board. Inclusion criteria for the groups were identical: age 18 or older, OA in one or both knees, joint-space narrowing or osteophyte formation on standing knee radiographs (Kellgren-Lawrence grade 2 or higher), and persistent pain despite best medical therapy. No clinical or radiographic degree of severity was disqualifying, other than the patient had to be ambulatory. Exclusion criteria for the groups were identical: pregnancy, nursing, implanted electronic device, or infectious or inflammatory arthritis. Outcome measures for the groups were identical: patient global assessment of disease activity in the study knee, patient assessment of pain intensity in the past 48 hours, pain on walking on a flat surface, pain on going up or down stairs, pain while sleeping at night, assessment of pain and associated symptoms in study knee, and physician global assessment. Efficacy outcomes were measured on a 5-point Likert scale (1 = no symptoms, 5 = very severe symptoms). Evaluations were done at baseline and at 1, 3, 6, and 12 months of treatment.

Figure 1 shows the BioniCare stimulator (Figure 1A) and the BioniCare stimulator combined with the OActive unloading brace (Figure 1B). The brace is a single upright lateral unloading brace that can be adjusted to push and unload the medial compartment or to pull and unload the lateral compartment. The lateral application is important in patients who require bilateral bracing, as medial components would interfere with walking. The stimulator is a portable, battery-operated unit capable of delivering 0V to 12V at a frequency of 100 Hz. It delivers a monophasic, exponentially decaying spiked signal...
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The stimulator provides subthreshold pulsed electrical fields by noninvasive means. Each patient self-adjusts the voltage to a level just below perceptible voltage. An embedded, tamperproof timer records the number of hours of actual use.

The positioning of the proprietary electrodes within the unloading brace has been optimized with use of finite element analysis to ensure delivery of the signal at a voltage optimal for penetrating the periarticular tissues and to stimulate the knee cartilage. Signal strength has to be sufficient to positively affect the chondrocytes, but not so strong as to damage them.

Statistical Analysis

Statistical analysis was independently performed by Novella Clinical (Morrisville, North Carolina). A generalized linear model repeated-measures analysis of change from baseline was performed, with sex, age, treatment (stimulator with brace vs without brace), cumulative device use at each follow-up (1, 3, 6, and 12 months), and baseline score of the 7 outcome measures as predictors of the model. Baseline and final weeks’ efficacy data were analyzed to compare results within centers and to determine any center × device interactions.

In clinical trials, group-level results are usually reported as means and standard deviations of the change in score. We have done so here as well. However, because this practice does not always provide clinically significant relevance, most readers do not find it meaningful. As a statistically significant difference is mostly a matter of sample size, the most difficult issue is whether an observed or estimated difference is clinically important. In other words, statistical significance is not equivalent to clinical significance. To provide more clinically relevant results, we also report the percentage of patients who have improved by 20% or more and the percentage of those who have improved substantially, by 50% or more. This additional information can help clinicians decide whether the treatment should be used.

Results

Demographically, the study and control groups were comparable. Mean age was 69.3 years (range, 23-97 years) for the study patients, who received the combined treatment (stimulator and brace), and 61.2 years (range, 32-93 years) for the control patients, who received only stimulator treatment. The difference was statistically significant (P<.001). However, one would expect that the older patients (combined treatment) would be less responsive and that the benefit of the combination treatment might even be greater in younger patients. Seventy-three percent of study patients and 67% of control patients were female. The 2 groups were comparable with respect to all 7 outcome measures at baseline. In addition, the groups’ cumulative hours of stimulator treatment were similar. Mean duration of use, recorded by the tamperproof timer, was 988.8 hours for the study group and 1082.2 hours for the control group.

Seventeen (7.6%) of the 225 study (combined-treatment) cases and 53 (18.3%) of the 289 control cases were treatment failures because of inadequate clinical response. The difference was clinically and statistically significant (P<.001). Forty-one study patients (18%) and 55 control patients (19%) exhibited these clinical failures.

Table I. Change From Baseline in Treatment Effects for Stimulator Only Versus Stimulator Combined With Unloading Brace

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>Treatment Group</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity in past 48 hours</td>
<td>Stimulator</td>
<td>-0.6734</td>
<td>0.0401</td>
<td>281.52</td>
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<tr>
<td></td>
<td>Stimulator plus brace</td>
<td>-0.8794</td>
<td>0.0321</td>
<td>748.79</td>
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<td>Physician global assessment</td>
<td>Stimulator</td>
<td>-0.7465</td>
<td>0.0423</td>
<td>310.94</td>
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<tr>
<td></td>
<td>Stimulator plus brace</td>
<td>-0.8392</td>
<td>0.0309</td>
<td>735.83</td>
</tr>
<tr>
<td>Pain and associated symptoms</td>
<td>Stimulator</td>
<td>-0.5503</td>
<td>0.0391</td>
<td>198.54</td>
</tr>
<tr>
<td></td>
<td>Stimulator plus brace</td>
<td>-0.7368</td>
<td>0.0317</td>
<td>539.48</td>
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<tr>
<td>Patient global assessment</td>
<td>Stimulator</td>
<td>-0.6253</td>
<td>0.0426</td>
<td>215.88</td>
</tr>
<tr>
<td></td>
<td>Stimulator plus brace</td>
<td>-0.8320</td>
<td>0.0318</td>
<td>685.24</td>
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<td>Pain while sleeping at night</td>
<td>Stimulator</td>
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<td>0.0426</td>
<td>292.45</td>
</tr>
<tr>
<td></td>
<td>Stimulator plus brace</td>
<td>-0.7581</td>
<td>0.0346</td>
<td>478.99</td>
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<tr>
<td>Pain on going up or down stairs</td>
<td>Stimulator</td>
<td>-0.6497</td>
<td>0.0441</td>
<td>216.95</td>
</tr>
<tr>
<td></td>
<td>Stimulator plus brace</td>
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<td>0.0374</td>
<td>603.65</td>
</tr>
<tr>
<td>Pain on walking on a flat surface</td>
<td>Stimulator</td>
<td>-0.5535</td>
<td>0.0417</td>
<td>176.24</td>
</tr>
<tr>
<td></td>
<td>Stimulator plus brace</td>
<td>-0.7654</td>
<td>0.0343</td>
<td>499.19</td>
</tr>
</tbody>
</table>

*All P<.001.
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Patients (19%) were lost to follow-up. Forty-four control patients (15%) developed rashes under electrodes. Most rashes disappeared after a few days of interrupted stimulator use. Fourteen (5%) of the 289 control patients discontinued participating in the study because of the rashes. Because of improved electrode technology, only 14 study patients (6%) developed irritations or rashes, and only 1 of these patients discontinued participation. Brace-fitting problems that required adjustment occurred in 22 (9.8%) of the 225 study patients, and 11 (50%) of the 22 discontinued participation. Neither study reported any adverse effects of the stimulator on the internal organs.

Use of the stimulator, alone or combined with the brace, provided statistically significant results (P<.001) on all 7 outcome parameters (Table I). There was no significant difference for patients with varus or valgus deformities of the knees. At baseline, there were no discernible factors that identified treatment nonresponders. Combined treatment was superior to stimulator-only treatment in patient global assessment of disease activity (P<.001), OA knee pain and symptoms (P<.001), pain in past 48 hours (P<.001), pain on walking on a flat surface (P<.001), and pain on going up or down stairs (P<.001) (Table II). The treatments were equally effective with respect to pain while sleeping at night and physician global assessment, but combined treatment was favored in both outcomes.

At 1-month evaluation, more patients achieved significant clinical improvement, at least 20%, with combined treatment than with stimulator-only treatment. For OA pain and symptoms, 50% of combined-treatment patients and 35% of stimulator-only patients obtained significant clinical improvement (P = .039); for pain on going up or down stairs, it was 56% of combined-treatment patients and 37% of stimulator-only patients (P = .005); and for pain walking on a flat surface, it was 50% and 32% (P = .013). Although the treatments were comparably effective for the other 4 outcome parameters, results in all instances favored combined treatment.

At 3-month evaluation, more patients achieved significant clinical improvement, at least 20%, with combined treatment than with stimulator-only treatment. For pain in the past 48 hours, 67% of combined-treatment patients and 49% of stimulator-only patients obtained significant clinical improvement (P = .032). For pain on going up or down stairs, it was 67% and 49% (P = .005); and for pain walking on a flat surface, it was 61% and 47% (P = .006). Although the treat-
ments were comparably effective for the other 3 outcome parameters, results in all instances again favored combination treatment.

At 6-month evaluation, more patients achieved significant clinical improvement, at least 20%, with combined treatment than with stimulator-only treatment. For pain in the past 48 hours, 75% of combined-treatment patients and 54% of stimulator-only patients obtained significant clinical improvement (P<.001); for physician global assessment, it was 74% of combined-treatment patients and 58% of stimulator-only patients (P = .002); for pain going up or down stairs, it was 69% and 54% (P = .005); and for pain walking on a flat surface, it was 67% and 47% (P<.001). Although the treatments were comparably effective for the other 3 outcome parameters, results in all instances again favored combination treatment.

At 12-month evaluation, more patients achieved significant clinical improvement, at least 20%, with combined treatment than with stimulator-only treatment (Table III). For pain while sleeping at night, 72% of combined-treatment patients and 57% of stimulator-only patients obtained significant clinical improvement (P = .002); for pain going up or down stairs, it was 69% and 54% (P = .005); and for pain walking on a flat surface, it was 67% and 47% (P<.001). Although the treatments were comparably effective for the other 5 outcome parameters, results in all instances favored combination treatment. A mean of 72% of combined-treatment patients (range, 68%-76%) and a mean of 63% of stimulator-only patients (range, 55%-70%) obtained significant clinical improvement on all 7 outcome parameters (P<.001). Thus, the vast majority of patients after a year of treatment (stimulator with and without brace) obtained significant clinical and statistically significant improvement on all 7 primary outcome parameters, uniformly favoring the combination treatment.

Also significant is the number of patients who obtained substantial clinical improvement, at least 50%, after 12 months of treatment. The study and control treatments were comparably effective, but again the combination treatment
was favored on all 7 outcome parameters (Table IV). A mean of 40% of combined-treatment patients (range, 35%-51%) and a mean of 32% of stimulator-only patients (range, 28%-39%) obtained substantial clinical improvement, at least 50%, on all 7 outcome parameters after 12 months (P = .005).

We expected that there would be an additive treatment benefit of combining stimulator and brace and that it would last until the full benefit of stimulator use was obtained, after 6 to 9 months. We were surprised to find some synergistic action between stimulator and brace, as the advantage continued throughout the study and was apparent even after 1 year of treatment (Figures 3-5). Unlike most medications used to treat knee OA, the stimulator exhibited no ceiling effect for the duration of the study (the longer patients used the device, the larger its effects). Thus, the benefits of stimulator treatment increased in dose–response fashion throughout the study.

Discussion

In 1990, Lippiello and colleagues13,21 studied the BioniCare pulsed electrical stimulator in the treatment of osteochondral defects in rabbits. Full-thickness cartilage bore defects (1.2 and 3.2 mm in diameter, 6 mm deep) and lacerative saw defects (1 mm wide, 3 mm deep, 1 cm in length) were created. The stimulator-treated cartilage defects healed with hyaline-like cartilage material and without any pannus formation; the placebo-device–treated control knees demonstrated material resembling fibrocartilage with no safranin O staining, and inflammatory pannus formation (Figure 6). Subsequently, Lippiello and colleagues13,21 demonstrated that, when human chondrocytes are exposed to the stimulator signal for 2 hours, type II collagen decreases by 54% and aggrecan by 50% (Figure 7). Although the histologic changes in articular cartilage related to BioniCare treatment have not been studied in human knee OA, the implications of these studies for treating OA in humans is compelling.

Successful preclinical trials were followed by a prospective, double-blind, placebo-controlled, randomized multicenter trial in 78 patients who had derived inadequate benefit from NSAID and/or analgesic therapy. Patients remained on stable background therapy. There was significant improvement in patients treated with the active stimulator versus the placebo device in the entire intent-to-treat population for all 3 primary outcome measures: physician global assessment (P = .02), function (P = .04), and pain and associated symptoms (P = .04). Improvements in 2 secondary outcome parameters, morning stiffness and range of motion, were also significantly larger for the stimulator group than for the placebo group (P<.05 for both). The study was independently analyzed by the US Food and Drug Administration, which in 1997 cleared the BioniCare device for “use as adjunctive therapy for the treatment of knee OA for the improvement of pain and associated symptoms of knee OA and for overall improvement of the knee as assessed by the physicians global evaluation.”22

Later, a confirmatory, 3-month, double-blind, placebo-controlled, randomized study of BioniCare treatment was conducted on 58 patients who had moderate to severe knee OA and insufficient benefits from conventional therapy.23 All patients had Kellgren-Lawrence stage 3 or 4 radiographic changes. As in the first study, best medical therapy was maintained the month before and then throughout the study, rather than being withdrawn. Significant improvement was found in the entire intent-to-treat population for patient global assessment (P = .03), patient pain on a 100-mm visual analog scale (P = .03), WOMAC (Western Ontario and McMaster Universities) stiffness (P = .03), WOMAC function (P = .01), and

Figure 6. Photomicrograph of repair of 1.2-mm osteochondral defect in unstimulated animal sacrificed at 8 weeks (safranin O). (A) Short arrows indicate right margin of wound; long arrows indicate extrusion-like appearance of fibrous tissue forming pannus over articular cartilage. (B) Similar section from animal stimulated for 40 hours. Arrows indicate margin of defects. Note extensive remodeling in subchondral bone beneath defect site and presence of cartilage islands stained with safranin O (Cartilage Islands).

Figure 7. Increased matrix macromolecule production in human chondrocytes with BioniCare stimulator versus decreased production with transcutaneous electrical nerve stimulation (TENS).
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Figure 8. Percentage of 103 patients who were treated with BioniCare stimulator for 11 months (vs 42 matched controls) and who deferred total knee arthroplasty by year.

Figure 8. Percentage of 103 patients who were treated with BioniCare stimulator for 11 months (vs 42 matched controls) and who deferred total knee arthroplasty by year.

Mont and colleagues led a 4-year, prospective, open-label, multicenter study of 157 candidates for total knee arthroplasty (TKA) and compared them with 102 historical controls matched on clinical and radiographic severity. After a mean of 11 months of treatment, 60% of stimulator-treatment patients versus 35% of patients given best therapy without stimulator treatment, deferred TKA surgery for at least 4 years. In patients with severe disease (Kellgren-Lawrence stage 4), 62% of those treated with the BioniCare device, versus 7% of those in the matched control group, deferred surgery for at least 4 years (Figure 8).

The present study clearly demonstrated that stimulator treatment alone or in combination with an unloading brace provided statistically significant and clinically relevant benefits on all 7 outcome parameters used (P < .001). It also clearly demonstrated that stimulator-and-brace combination was superior to stimulator-only treatment. For all observation points (1, 3, 6, and 12 months) and all 7 outcome parameters, significant clinical benefit (≥20%) was obtained by a higher percentage of combined-treatment patients than stimulator-only patients (72% vs 63%; P < .001); likewise, substantial clinical benefit (≥50%) was obtained by a higher percentage of combined-treatment patients than stimulator-only patients (40% vs 32%; P = .005). This was also evident from the fact that there were more than twice (18.3% vs 7.5%) as many treatment failures in the stimulator-only group than in the combined-treatment group. This is an indication of increased adherence and increased efficacy with the combination treatment.

A weakness of this investigation is that one study ended in 2005 and the other began in 2010. We think the gap is compensated for by the large number of patients treated in each group, and by the groups’ comparable demographics, rheumatologists and orthopedic surgeons, and disease severity, as evidenced by the outcome measures being equivalent at baseline. Moreover, no new treatment modality was introduced between studies, and corticosteroid injections and viscosupplementation were specifically prohibited from both. Tamperproof timers demonstrated comparable treatment duration with respect to the stimulator in both groups.

Both the magnitude of differences and the synergistic effect would indicate that there is a real treatment difference in combining the stimulator with the unloading brace. We have 3 hypotheses. First, the unloading brace may decrease the friction and the subsequent wear of the cartilage with weight-bearing. Second, placing the electrodes inside the brace maintains proper positioning throughout the treatment period. Third, stimulator treatment provides a capacitive coupled exogenous electrical signal similar to the endogenous signal of weight-bearing. When stimulator treatment is used alone, it is delivered with a night wrap while the patient is sleeping, and there is no concomitant endogenous signal created. When stimulator and brace are combined, the exogenous signal combines with the endogenous signal of weight-bearing, and the effect is somehow synergistic.

Whatever the mechanism, the long-term clinical studies of stimulator treatment have shown reductions in pain and associated symptoms, improved function, overall improvement in OA knees, and substantial deferral of TKA for at least 4 years. In the present study, stimulator–brace combination treatment clearly produced substantial improvement much more rapidly than stimulator-only treatment did. Thus, patients remained on the device long enough to achieve overall knee improvement. It is thought that rapid and increased improvement with stimulator–brace combination treatment should improve adherence and increase the ability to defer TKA surgery.

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References