Clinical Trials of BION™ Microstimulators
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Abstract
BIONs have now been used in clinical trials for more than two years. BIONs are injectable microstimulators that can be used to provide exercise and return of function to paralyzed or weak muscles. Electrical stimulation with BIONs has shown to be effective at reversing sub-acute shoulder subluxation after a stroke and improving function of patients with unilateral osteoarthritis of the knee. A third study, aimed at reversing chronic shoulder subluxation after a stroke, is just starting.

1. Introduction
BIONs are microminiature, single channel stimulators that can be injected into muscles. They receive power and individually addressable commands from an external magnetic field. The convenience of using BIONs has proven to be an important advantage for therapeutic electrical stimulation of muscles atrophied by disuse. The implantation is usually done as an outpatient injection and lasts about 20 minutes. Stimulation can start less than a week after implantation. BIONs have been shown to remain in place in animal and human tissue for years and to trigger only minimal foreign-body reaction [1,2]. Patients in the hospital for stroke rehabilitation and those living at home have found the system simple to use and compliance has been high. The initial applications for BION use were chosen for their simplicity, their therapeutic effect and the need to activate either large or deep muscles. Last year we presented preliminary data on the Canadian and the Italian trials. We now present more conclusive data, as well as preliminary data from the American trial.

2. Method
For the sub-acute shoulder subluxation study, hemiplegic patients 3-12 weeks post-stroke are randomized into a control or treatment group. Subjects in the treatment group are implanted with a single BION in each of the middle deltoid and supraspinatus muscle and receive stimulation daily for 6 weeks in addition to their regular therapy. This is followed by a ‘non-stimulation’ period of 6 weeks, designed to study whether the effects of stimulation (if any) have some permanence. In the control group, only traditional therapy (such as passive rehabilitation exercises) is offered for a 6 week period, after which the subjects are offered BION therapy if their shoulder is subluxed. During the trial, all subjects are assessed every 3 weeks for manual subluxation, arm strength, arm range of motion, stimulation thresholds (current and pulse width), and every 6 weeks for subluxation by X-ray, arm function, and pain (Visual Analogue Score).

For the chronic shoulder subluxation study, the subjects must have had the stroke more than 6 months before they enroll in the study. The stability of the subluxation in the chronic condition permits the use of a longitudinal, repeated measures design in which all subjects receive BION stimulation therapy. The stimulation paradigm is similar to the one described above for the sub-acute shoulder subluxation study. At the end of the 6 weeks of treatment, all subjects in whom the subluxation has not decreased significantly will be switched to a more intensive therapy in which subjects will be treated with 8
hours of stimulation per day, a paradigm that has been seen to work in a previous study [3].

The osteoarthritis knee study also has a longitudinal repeated-measures design. Subjects are first observed for 12 weeks to determine their baseline state. They are evaluated with the Western Ontario-McMaster (WOMAC) knee function scale, Knee Society Function tests and pain (by Visual Analogue Scale or VAS). Muscle cross-sectional areas are assessed using MRI. After baseline has been established, the subjects receive a BION implanted next to the femoral nerve, in the groin area.

In all of these studies, stimulation starts with 3 10-minute sessions per day, increasing gradually to 30 minutes per session. We use low frequency (2-5pps) trains of stimuli (2-5s on/1-3s off) at an intensity sufficient to recruit most or all of the motor units in the target muscles (typically 2-8 times motor threshold).

3. Results

All subjects implanted with BIONs have been satisfied with the simple implantation procedure, absence of complications and easily self-administered therapy. Only one subject has to be removed from the study, an elderly man who suffered from a loss of short-term memory, presumably due to his stroke, and was not compliant with his sub-acute shoulder subluxation therapy. One subject asked to have a BION removed after her participation in the osteoarthritis trial had been completed; she experienced unpleasant sensation in her groin intermittently when sitting (not during stimulation). The BION was removed in a short surgical procedure lasting approximately 30 minutes. After discussion with the surgeon, it was concluded that the BION had been oriented in a manner that might result in pressure on the adjacent tissues when the hip was flexed.

In the sub-acute subluxation trial, a total of 8 subjects had completed the trial at the end of December 2001. Of those, 3 had been randomized as experimental, and 5 as control subjects. Of the 5 control subjects, all but one have chosen to be implanted at the end of their control period. Data from a total of 5 control subjects and 5 stimulated subjects (both control and experimental) are available. Subluxation of the hemiplegic shoulder is the primary outcome measure. For both manual and radiological measurements, significant decrease was found between subluxation levels before and after 6 weeks of BION therapy (p < 0.05). If no BION therapy was administered, no significant difference was found between original measurements (at the beginning of the trial) and 6 weeks later (figure 1). Other outcome measures did not show significant changes over the 6 weeks of BION therapy.

In the knee osteoarthritis trial, three subjects have completed the study. As of the end of 2001, three more subjects were enrolled in the study, two having been implanted and one being studied for baseline results. Significant improvement of knee score (Knee Society Score) and decrease of pain were found after 12 weeks of BION therapy for the 3 patients who have completed the trial (p<0.05) (Figure 2). Improvement of the knee function score was also seen over the 12 weeks of BION therapy, although the difference was not found to be significant with only 3 subjects. WOMAC scores improve significantly (p<0.05) between implant date and both 6 and 12 weeks of stimulation later (Figure 2). One of these subjects has cancelled her scheduled knee replacement surgery. Although she may need to consider this option again as her knee degenerates further, the improved function and decreased pain are sufficient to avoid surgery. She still uses BION therapy once a day. Cross-sectional areas of quadriceps muscles have been measured on MRI scans and analyzed for patient 1 of this study. No significant difference was seen between the relative cross-sectional areas of the affected limb (relative to the

![Figure 1: Shoulder subluxation, as measured on X-ray, for subjects without and with stimulation of the deltoid and the supraspinatus muscles.](image-url)
In the chronic shoulder subluxation study, the first patient is scheduled to be implanted with BIONs in January as a 'pilot' patient. Results should be available by June 2002.

4. Discussion

Although these are preliminary results of two clinical trials with few patients, significant improvement was seen in some of the outcome measures for both studies. As expected, these results are similar to those achieved in prior studies in which electrical stimulation was delivered transcutaneously. Stimulation thresholds remain constant over time as reported previously [4], indicating a stable foreign body reaction around and little or no migration of the BIONs (also confirmed on X-rays). Autopsy tissue is being analyzed from one of the stroke patients who died of unrelated causes after two years of BION treatment.

More importantly, BION patients were compliant with their therapy and found it pleasant to receive. Patients self-administered the therapy at home, avoiding the cost of a medical professional administering the therapy and making it a practical treatment for patients who may need it chronically. Other applications of BIONs to treat paralysis and disuse atrophy are under development.

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References