

CLINICAL TRIALS OF BIONS™ FOR THERAPEUTIC ELECTRICAL STIMULATION

F.J.R. Richmond¹, G.E. Loeb¹, A.C. Dupont¹, S.D. Bagg², J.L. Creasy²,
C. Romano³ and D. Romano³

¹A.E. Mann Institute for Biomedical Engineering, University of Southern California
Los Angeles, CA 90089, USA; <http://ami.usc.edu>

²Queen's University, Kingston, Ontario K7L 3N6, Canada

³Istituto Ortopedico Gaetano Pini, Milan 20122, Italy

Abstract - BIONS™ are individually addressable, single channel electrical stimulators that can be injected into one or more muscles through a 12-gauge hypodermic needle. They receive power and command signals from an externally worn RF transmission coil. Two clinical trials are underway to determine their safety and efficacy for strengthening atrophic muscles associated with stroke (7 patients accrued; 6 implanted) and chronic osteoarthritis of the knee (5 patients accrued; 3 implanted). In both studies, BIONS have proven easy for the clinician to implant and for the patients to use. Thresholds for recruitment of muscle contractions have remained stable and no adverse effects have been reported. Patients generally like the stimulation and most have elected to continue stimulation after the prescribed study period. Stimulation at low frequencies for a total of about 1 hour/day has produced demonstrable reversals of muscle atrophy as measured by imaging. In patients with radiological subluxation of the shoulder, the subluxation has been reduced. Preliminary indications suggest also that chronic pain has been reduced and locomotor function has improved in patients with knee osteoarthritis. Extensions of these studies to broader categories of patients and clinical problems are underway.

Keywords - stroke, shoulder subluxation, knee osteoarthritis, electrical stimulation, implants

I. INTRODUCTION

Therapeutic electrical stimulation is an efficacious tool to strengthen paralyzed or paretic muscles. However, such methods are not adopted routinely for the treatment of most patients because of limitations in the available technology. Clinical instrumentation for transcutaneous electrical stimulation is readily available but it requires careful placement of electrodes and adjustment of stimulation intensity for each treatment session. It also tends to generate unpleasant cutaneous sensations at intensities sufficient to recruit underlying muscles. Percutaneous intramuscular wires are useful for research but pose unacceptable risks of dislodgment, infection and breakage for general or long-term use. Fully implanted multichannel electrical stimulators are expensive and require surgical procedures that are unacceptable for many elderly or chronically ill patients.

The recent introduction of radio-frequency controlled, injectable microstimulators has provided a novel method to deliver electrical stimulation in a way

that circumvents some of the problems associated with conventional stimulation systems. The device we have developed (named BION™ for BIONic Neuron) is a self-contained, hermetically sealed, single-channel electrical stimulator (2 mm diameter x 16 mm long) that can be injected into a muscle through a 12-gauge hypodermic needle. Power and digital command signals are transmitted across the skin to one or more BIONS by inductive coupling of a 2 MHz AM carrier from an externally worn coil. Each BION has its own digital address and responds to a command by generating a monophasic, capacitively-coupled stimulus pulse with regulated current (0-30 mA in 2 ranges of 16 steps each) and pulse width (2 - 514 μ s in 512 linear steps). The extensive technology development and preclinical testing *in vitro* and in acute and chronic animals have been described elsewhere [1], [2], [3]. In this communication, we describe the early results of two clinical trials in which electrical stimulation of weakened muscles has been used to improve the functional capabilities and decrease the pain associated with shoulder and knee joint pathologies.

II. TREATMENT OF SHOULDER SUBLUXATION

Shoulder subluxation is a common complication of stroke because the weight of the pendant unsupported arm exerts chronic traction that pulls the head of the humerus out of the shallow glenoid fossa. Previous studies using transcutaneous or percutaneous stimulation have suggested that electrical stimulation of shoulder muscles can be efficacious in reducing the degree of shoulder subluxation in stroke survivors. In this randomized two-arm study, subjects were entered into the trial within eight weeks after a stroke that had resulted in hemiparesis, followed by unilateral shoulder subluxation. Subjects were required to have no other electronic implants, to not have severe hemineglect, to be medically stable, and to be mentally capable of carrying out the therapy independently. This report describes results in six subjects who have completed the trial; an additional subject has been implanted with BIONS but is still in early stages of therapy. In this trial, subjects in the experimental group (n = 3) were implanted with two BIONS in deltoid and supraspinatus muscles, respectively. These devices were used to stimulate muscles using trains of 5 pulses/sec (10 sec on, 5 sec off) for 1-1.5 hours per day (3 20-30 minute blocks) for six

Report Documentation Page

Report Date 25OCT2001	Report Type N/A	Dates Covered (from... to) -
Title and Subtitle Clinical Trials of Bions for Therapeutic Electricalstimulation	Contract Number	
	Grant Number	
	Program Element Number	
Author(s)	Project Number	
	Task Number	
	Work Unit Number	
Performing Organization Name(s) and Address(es) A.E. Mann Institute for Biomedical Engineering, University of Southern California Los Angeles, CA 90089	Performing Organization Report Number	
Sponsoring/Monitoring Agency Name(s) and Address(es) US Army Research Development & Standardization Group (UK) PSC 803 Box 15 FPO AE 09499-1500	Sponsor/Monitor's Acronym(s)	
	Sponsor/Monitor's Report Number(s)	
Distribution/Availability Statement Approved for public release, distribution unlimited		
Supplementary Notes Papers from the 23rd Annual International conference of the IEEE Engineering in Medicine and Biology Society, October 25-28, 2001, held in Istanbul, Turkey. See also ADM001351 for entire conference on cd-rom.		
Abstract		
Subject Terms		
Report Classification unclassified	Classification of this page unclassified	
Classification of Abstract unclassified	Limitation of Abstract UU	
Number of Pages 4		

weeks. Relatively low frequency stimulus trains (5pps) were employed, as suggested by studies of the stimulation parameters required to prevent disuse atrophy in a rat model [4]. Typically the stimulation program began with relatively short (10 minute) stimulation periods, 3 times a day, at strengths sufficient to produce only modest contractions. The period of stimulation was gradually increased to approximately 30 minutes (3 times a day), and the strength of the contraction was increased to produce strong contractions within the tolerance of the subject. Following this six-week treatment period, stimulation was discontinued for the next six weeks to determine whether subluxation would recur. At the end of the trial, subjects were allowed the choice of reinitiating stimulation if they wished. Subjects in the control group were not implanted initially with devices but were offered the opportunity to have implanted devices at the end of six weeks of observation under conventional treatment for subluxed shoulder. Two of three control subjects elected to have device implantations at the end of the control period. The protocol used to treat and assess these late-entering subjects was the same as that for experimental subjects.

In all subjects shoulder subluxation was the primary outcome variable and was assessed by measuring vertical displacement of the humeral head out of the glenoid fossa from x-rays (45° oblique AP). Several secondary outcome measures were also assessed. Thicknesses of both stimulated and matched contralateral muscles were measured by ultrasound at two points along the width of each muscle. These points were marked by small tattoo dots at the initial ultrasound session so that the same sites could be measured from one observation to another. In addition, the active and passive range of motion, force, shoulder pain (as measured using a visual analogue scale) and arm function were measured.

Results are currently available for six subjects who have completed therapy with BIONs. None of the patients experienced problems with the implantation or daily use of the devices. The patients tolerated the 10-20 minute implantation procedure well, and showed no evidence of discomfort or inflammation. All subjects in which both deltoid and supraspinatus were stimulated achieved similar subluxation reduction, regardless of whether they were admitted initially to the experimental or control group (Fig. 1).

Results in one patient with only deltoid stimulation were different. This patient began the trial with less subluxation than the other subjects and the degree of his subluxation did not change appreciably.

Subjects generally showed a thickening of stimulated muscles over the six weeks of stimulation, although the ultrasound measures showed some variability that was thought in part to reflect difficulties of imaging exactly the same region from one examination to another; this is believed to be due to the difficulty of obtaining a well-controlled angle between the muscle surface and the ultrasound probe. After the six-week stimulation period the gain in muscle thickness tended to remain. In contrast, in patients

without electrical stimulation, muscles typically became thinner (Fig. 2).

Thresholds for muscle stimulation (measured as charge, the product of current and pulse width) were recorded over time to gauge whether devices were moving or becoming excessively encapsulated. Implants that were in place for more than 180 days prior to final testing (range: 181-539 days) had thresholds at least as low as those measured during the first 30 days after implantation (Fig. 3).

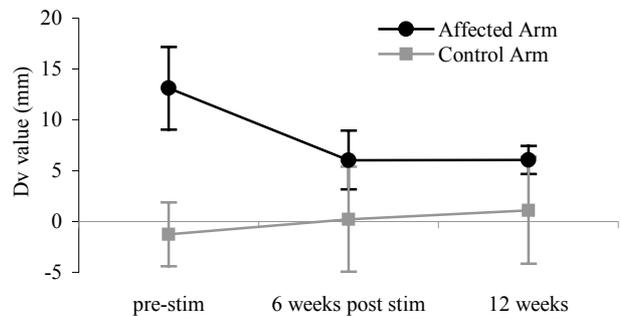


Fig. 1: Subluxation index (Dv = vertical displacement of the humeral head in the glenoid capsule) of subjects receiving stimulation for 6 weeks with a following 6 weeks off stimulation.

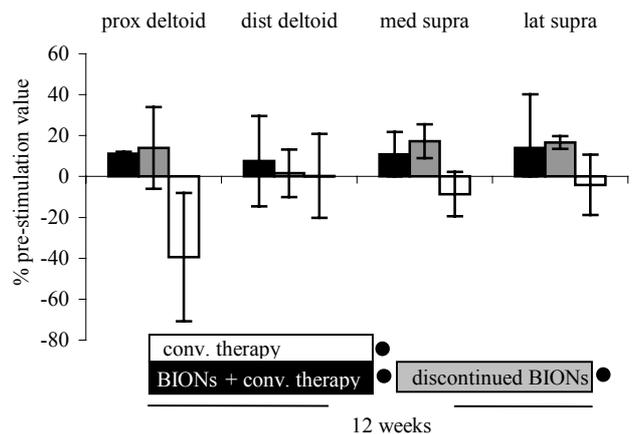


Fig. 2: Relative change in muscle thickness over time.

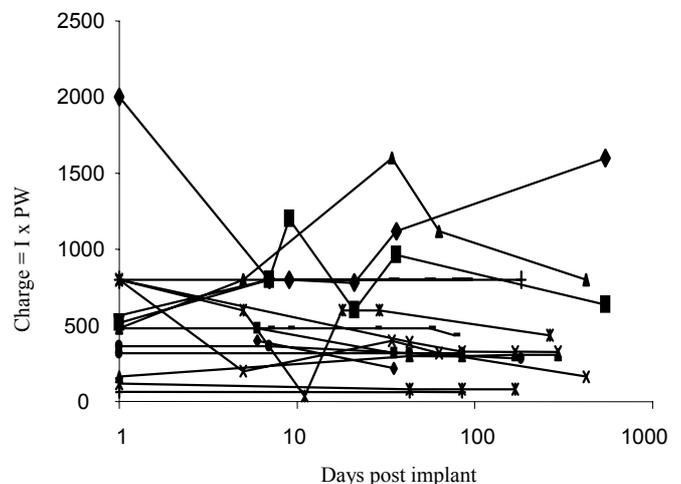


Fig. 3: Stimulation Thresholds (as charge) over time after implantation for each BION.

III. TREATMENT OF KNEE OSTEOARTHRITIS

Chronic knee osteoarthritis is a common problem of the senior population, manifested by pain, swelling, and diminished range of articular movement and function. Pain leads to decreased physical activity resulting in disuse atrophy, particular of the quadriceps muscles that normally protect the knee joint from further damage [5]. Exercises to strengthen the muscles are known to be effective [6] but compliance is often limited. In this trial, we used electrical stimulation applied by a single BION implanted near the common femoral nerve to exercise all of the heads of the quadriceps at high levels of recruitment but a low frequency to avoid excessive stress on the knee. To date, 5 patients have been enrolled in the study, with 3 having completed the 24 week course. Each patient is assessed before and after a 12-week control period to assure stability of their chronic condition, and again after 6 and 12 weeks of daily stimulation. The prestimulus control period provides the comparison values for each patient. Each subject is treated with 2-3 stimulation sessions of 10-30 minutes each day. Stimulation parameters are tailored to each patient and progress in intensity and duration as the patients build muscle strength and fatigue resistance. Generally, relatively low frequencies are used (5 – 13 pulses/sec) with an ON:OFF cycle of 2-5:1-3 secs. Primary outcome measures include WOMAC (Western Ontario McMaster Osteoarthritis Index) score and Knee Function scores (include pain and function values). Secondary outcome measures include muscle thickness (measured with MRI).

All patients found the sensation associated with muscle stimulation to be agreeable. There were no adverse events or complications related to the implants or exercise treatment. Threshold for eliciting muscle contractions remained stable over time (Fig. 3). WOMAC scores were significant lower ($p < 0.05$) at the end of the 12-week stimulation period than at the beginning, indicating better function and lower pain levels in the subjects (Fig. 4).

The Knee Society Pain score increased significantly ($p < 0.05$) from pre-stimulation values at the 12-week point, indicating more pain-free movement. A similar trend in Knee Function was not statistically significant (Fig. 4). Muscle thickness of subjects 1 and 2 showed an increase when data from before stimulation therapy and after 12 weeks of stimulation were compared (Fig. 5). Muscle thickness data from subject 3 had not been processed at the time of writing.

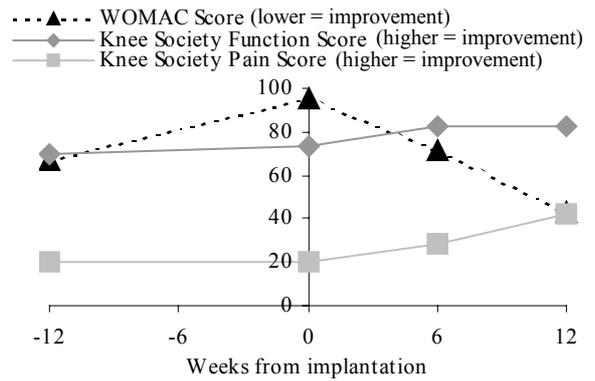


Fig. 4: Primary outcome measures in knee osteoarthritis study (N=3)

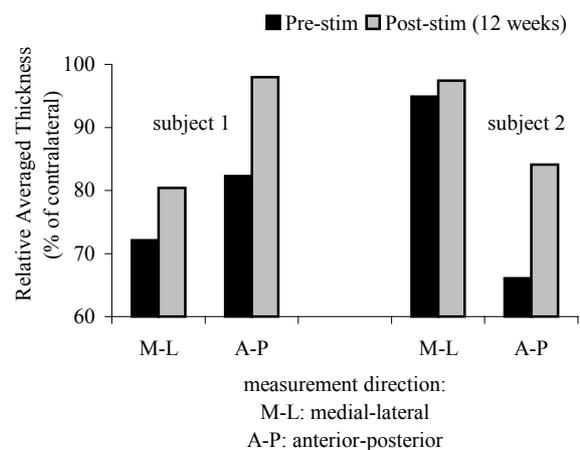


Fig. 5: Rectus Femorus Thickness (from MR scans)

IV. STABILITY AND EASE-OF-USE

Most subjects found the application of their treatment to be simple and convenient. In one patient continuing therapy after completion of the study, we found that one session of 15 minutes per day was sufficient to maintain good alignment of his shoulder. This subject also found that one longer session each day fit better in his lifestyle than two shorter sessions.

The external controller for the BIONs (called a Personal Trainer™) tracks its actual daily usage by the patient; this information is available to the clinician at each follow-up visit. So far in the shoulder subluxation trials, compliance was only problematic in one subject who had short-term memory problems. This subject has withdrawn from the trial: his subluxation has not been reduced.

A common concern with implanted devices has been the possibility that devices might migrate with time. In previous animal experiments of up to 13 months, there was no evidence of migration and the BIONs appeared to be well-anchored within the muscles by a matrix of endomysial connective tissue around the neck of the electrodes at both ends of the devices. Results in these subjects also suggested that little if any migration had occurred. X-rays showed that devices continued to be found in comparable locations over time. As well, thresholds in all subjects for both studies were stable up to almost 1.5 year after implantation, indicating that there is

no change in either the location of the devices or level of foreign body reaction around each device.

V. DISCUSSION

This preliminary evidence suggests that stimulation with injected BIONs is a useful and well-tolerated approach to exercising paralyzed muscles in stroke patients. The reduction of subluxation and the improvement in muscle size and strength is consistent with prior studies in which TES was applied to paralyzed shoulders via skin surface electrodes [7],[8]. Those studies, however, used much longer stimulation sessions (2-8h/d vs. ~1h/d) and higher frequencies of stimulation (10-20pps vs. 5pps). The present results are consistent with the results of a study of BIONs in an animal model of disuse atrophy [4], but more information is needed regarding optimal therapeutic parameters in humans. Present results lead us to be optimistic about the usefulness of even modest periods of electrical stimulation.

ACKNOWLEDGMENT

The clinical trials are funded by the Canadian Institute of Health Research and the Istituto Ortopedico Gaetano Pini. BION technology is provided by the A.E. Mann Institute

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