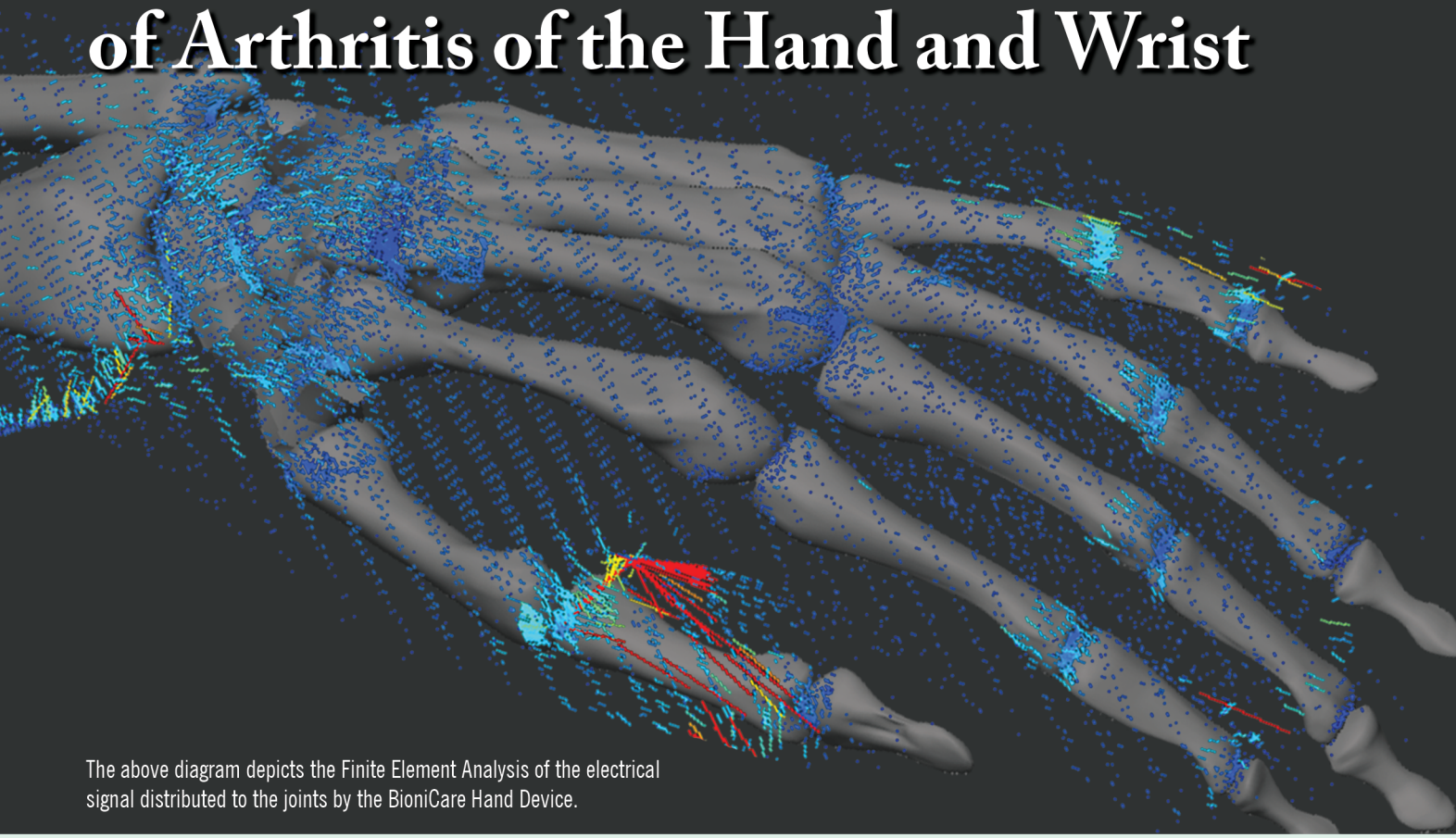
IMNG MEDICAL MEDIA

A Supplement to

Rheumatology News®

BioniCare® in the Treatment of Arthritis of the Hand and Wrist



The above diagram depicts the Finite Element Analysis of the electrical signal distributed to the joints by the BioniCare Hand Device.

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Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory, autoimmune disease that causes joint inflammation, cartilage destruction, and ligament weakness in involved joints. RA is further characterized by the formation of pannus, caused by synovial inflammation in areas of increased vascularity. Activated neutrophils from pannus release lysosomal enzymes and free radicals which destroy the articular surfaces. These destructive processes change the anatomy of the joint leading to a gradual loss of function.

The National Arthritis Data Workgroup estimated that 1,293,000 American adults aged ≥18 years (0.6%) had RA in 2005.[1] The prevalence in women is approximately double that in men. Also, the average age of persons with prevalent RA has increased steadily over time, from 63.3 years in 1965 to 66.8 years in 1995, suggesting that RA is becoming a disease of older adults. It has been estimated that over 70% of RA patients report hand and wrist dysfunction.

Pharmacotherapy for RA consists of nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, synthetic (nonbiologic) disease modifying antirheumatic drugs (DMARDs), biologic DMARDs, and combination drug therapy. The nonbiologic DMARDs are traditional small-molecule or synthetic DMARDs, such as methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. The biologic DMARDs, produced by recombinant DNA technology, target specific cytokines or their receptors, such as tumor necrosis factor-alpha (TNF-α) or the TNF receptor, interleukin-1 (IL-1), or interleukin-6 (IL-6) receptor. Other types of biologic DMARDs include B cell depleting agents and T cell costimulatory blockers.

Prior to the widespread use of methotrexate or the availability of targeted biologic agents, RA was associated with a high degree of economic loss, morbidity, and early mortality. As an example, almost 80% of patients in one center were severely disabled after 20 years of follow-up; an additional one-third had died.[2] Poor outcomes with conventional therapy led to the concept of effective treatment of newly diagnosed early aggressive disease to suppress ongoing inflammation and prevent joint injury.[3]

Guidelines concerning therapy for RA have been published by the American College of Rheumatology.[4] No treatment cures RA; therefore, the therapeutic goals are the remission of symptoms involving the joints, a return to full function, and the maintenance of remission with DMARD therapy.

Until the past decade, concern about the toxicity of the DMARDs has delayed their use in treating RA. Joint damage occurs early in the course of RA; 30% of patients have radiographic evidence of bony erosions at the time of diagnosis, and this proportion increases to 60% by 2 years.[5] Unfortunately, bony erosions and deformities are largely irreversible. Initiation of therapy with DMARDs within 3 months after the diagnosis of RA is crucial; a delay of as little as 3 months in the introduction of these medications results in substantially more radiographic damage at 5 years.[6,7] Thus, it is now accepted that the consequences of delaying therapy (joint destruction, disability, and early mortality) significantly outweigh the possible toxic effects from these agents.

Since observational trials have clearly identified methotrexate as the synthetic DMARD that is most likely to induce a long-term response, it is most often selected for initial therapy. It has demonstrated efficacy and durability, a long-term track record of acceptable toxicity, and low cost.[8] If patients continue to have active disease after 2 to 3 months of methotrexate at a dose of up to 20 to 30 mg per week, or if they cannot tolerate high doses of methotrexate despite folate replacement, the current standard practice is to add another DMARD to methotrexate.

Even with the range of therapies currently available, some patients still have poorly or incompletely controlled disease. This is particularly problematic when the hands and wrists are not controlled. Hand dysfunction is one of the major causes of disability in patients with RA.[9] In the hand, it commonly affects the wrist joint, metacarpophalangeal (MCP) joints, and proximal interphalangeal joints. Many RA patients experience difficulties performing basic activities of daily living and nearly 60% of patients are work disabled within 10 years of disease onset.[10]

RA hand surgery is divided into prophylactic and reconstructive procedures. Prophylactic procedures include tenosynovectomy, joint synovectomy, and tendon rebalancing. Extensor tenosynovectomy is recommended when synovitis persists for 3 to 6 months despite aggressive medical management.[11] For MCP joint synovitis, 6 to 9 months of medical management is recommended before considering surgery. Persistent, localized joint synovitis may benefit from synovectomy, but the long-term benefit of surgery in ameliorating joint destruction has not been shown in well conducted trials. The introduction of new RA medications has been quite effective in treating synovitis and the rate of synovectomy procedures is decreasing. These prophylactic procedures may delay the destructive RA processes, extending the useful life span of tendons and joints. Reconstructive procedures are often more complex than prophylactic procedures.

Reconstructive procedures include arthrodesis, arthroplasty, and tendon transfer. The wrist is the earliest and most frequent site of RA hand disease. Commonly there is radial deviation and ulnar translocation of the carpal bones. There could be dissociative lesions where the carpal bones separate from each other due to ligament ruptures. Depending on the involved part of the wrist joint, partial wrist arthrodesis can treat the diseased part while keeping the unaffected part still mobile. Partial wrist arthrodesis is more appealing than total wrist arthrodesis as it retains some motion. On the other hand total wrist arthrodesis is a predictable procedure and has a low complication rate. For patients with bilateral

wrist disease, arthrodesis is recommended in the dominant hand to maintain stability for gripping and power. The nondominant hand is treated with arthroplasty to maintain some joint motion needed for self-hygiene. Total wrist arthrodesis is contraindicated in patients with severe shoulder and elbow disease because patient needs may not be able to adapt to the loss of motion in all 3 joints. The wrist mobility with arthroplasty is traded for the predictability of pain relief and stability with arthrodesis. The MCP joint is the key joint for finger function. When one grips an object, the arc of motion is initiated at the MCP joint, then the PIP and the DIP joints. Therefore, motion at the MCP joints in the fingers must be maintained for adequate hand function. The RA patient with minimal pain and good hand function is best treated without an operation. When there is severe joint destruction, MCP arthroplasty should be considered.

Although RA is a common cause of debilitating hand deformities, the management of these deformities is controversial, characterized by large variations in the surgical rates of common RA hand procedures. A random national sample of 500 rheumatologists and 500 hand surgeons in the United States found that 70% of rheumatologists consider hand surgeons deficient in understanding the medical options available for RA, while 73.6% of hand surgeons believe rheumatologists have insufficient knowledge of the surgical options for RA hand diseases.[12] The 2 physician groups disagree significantly on the indications for commonly performed RA hand procedures such as metacarpophalangeal joint arthroplasty ($P < .001$), small joint synovectomy ($P < .001$) and distal ulna resection ($P = .001$). The largest divergence in attitudes involve small joint synovectomy: 49.8% of surgeons believe that progressive joint synovitis was the primary indication for surgical intervention compared with 12.9% of rheumatologists. Indeed, 34.7% of rheumatologists, compared with 1.8% of surgeons, believe that small joint synovectomy is never clinically indicated for rheumatoid patients.

Surgery of the rheumatoid hand has been shown to vary considerably across the United States. Procedure rates varied 9- to 12-fold for 3 procedure types: arthrodesis, arthroplasty, tenosynovectomy. The rate differences were not explained by the number of hand surgeons, disease prevalence, or disease composition of the states. It has been shown that variations in practice patterns often are caused by a lack of evidence-based medicine.[13] This significant variation across the United States probably reflects clinical uncertainty as well as disagreement among referring or treating physicians. A systematic review of the outcomes of MCP joint arthroplasty revealed that published studies on this procedure had inconsistencies in data reporting and a paucity of standardized hand function data.[14] In fact, only 19% of rheumatologists surveyed felt that high-quality information regarding surgical options and outcomes for rheumatoid hands was available. Thirty-four percent of rheumatologists versus 83% of hand surgeons agreed that MCP joint arthroplasty always or usually improves hand function ($P < .001$).[15] Both specialties agreed that function and pain are the main reasons why physicians recommend surgical reconstruction. Only 13% of rheumatologists versus 53% of hand surgeons believe that small-joint synovectomy delays joint destruction. Hand surgeons still lament that rheumatologists refer patients for hand reconstruction too little and too late.[16]

Whatever the discipline, it is important for all providers of care for RA patients to remember that first-line treatment of the RA hand aims to control the systemic disease. Any surgical intervention is futile without controlling the systemic inflammation, as surgical repairs cannot withstand the inflammatory challenge of uncontrolled disease.

In the past year, another option for patients with incompletely controlled rheumatoid hand disease has become available. This nonsurgical option consists of the application of the BioniCare technology, well-established in the treatment of osteoarthritis of the knee, to patients with RA of the hand and wrist. The initial rationale developed from the fact that a number of very specific electrical signals, including the BioniCare signal, were capable of reducing inflammatory cytokines in vitro.[17]

Material and Methods

The safety and effectiveness of stimulation from pulsed electrical fields using the BioniCare stimulator system was investigated for the treatment of RA of the hand (**Figure 1**).[18] Eighty-nine patients were enrolled in a prospective, multicenter, randomized, double-blind, placebo-controlled clinical

FIG. 1: BioniCare Hand System

study. Serial numbers of both active and placebo devices were provided to the US Food and Drug Administration (FDA) prior to commencement of the study. A randomization table was generated and maintained in a central location by an individual who had no contact with either the investigators or the patients. Placebo and active devices were indistinguishable to patients as the setup process was identical and only the placebo devices were internally programmed to shut off the subthreshold signal after several minutes of application. All study subjects had to be over the age of 20 years and required to meet the inclusion and exclusion criteria of the American College of Rheumatology (ACR) for RA. Patients in the active and placebo treatment groups were comparable, demographically (**Figure 2**). Additionally, patients were required to have active symptomatic synovitis of the treated hand despite best medical therapy. Background arthritis medications, both NSAIDs and DMARDs, were maintained constant for the 4 months prior to the study and throughout the study. The use of DMARDs, including methotrexate, NSAIDs, corticosteroids, and analgesics, is shown in **Figure 3**. There were no statistically significant differences in

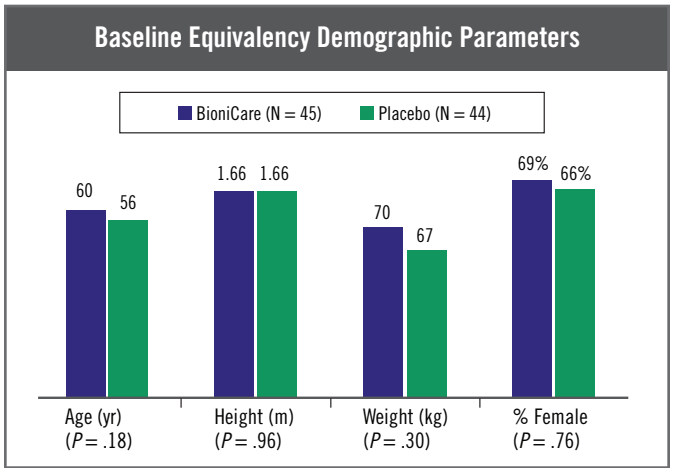

FIG. 2: Baseline Equivalency Demographic Parameters

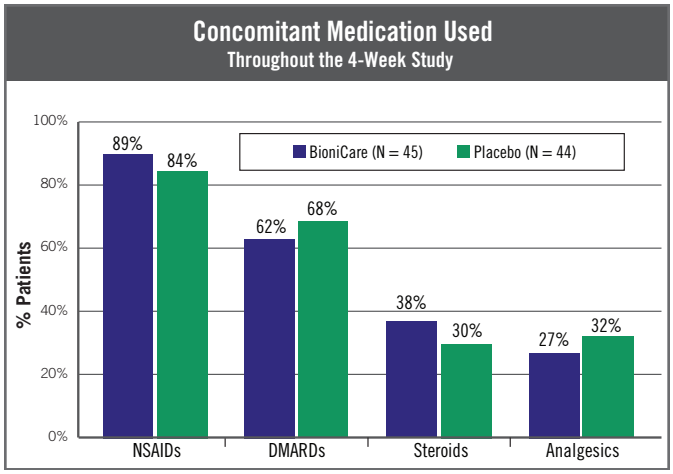

FIG. 3: Concomitant Medication Used Throughout the Study
Abbreviations: DMARD, disease modifying antirheumatic drug; NSAID, nonsteroidal antiinflammatory drug.

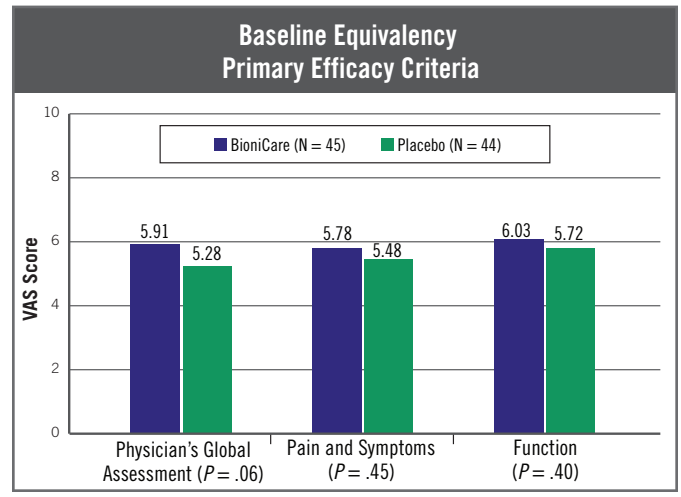

FIG. 4: Baseline Equivalency Primary Efficacy Criteria
Abbreviation: VAS, visual analog scale.

the use of any of these medications by treatment or by study sites. Patients with heart pacemakers or other implanted electrical devices, patients who were pregnant, patients who were nursing, and patients who were immediately postsurgical were excluded from the study. The BioniCare device was used for 8 (±2) hours daily for a 4 week treatment period. The primary outcome measures were the patient's evaluation of pain and symptoms, the patient's evaluation of function, and the physician's global assessment, all of which were measured on a standard horizontal visual analog scale. For outcome measures, scores from the 2 baseline visits were averaged to derive a baseline score. Improvement in scores of the baseline and percent improvement from baseline were determined for each of the post-baseline visits. The primary outcome measures were comparable in the active and placebo groups at baseline (**Figure 4**).

Statistical Methods

A targeted sample size of 80 patients was determined by assuming 30 completed patients in each group, with a 90% probability of detecting an effect size (difference in means of baseline minus final treatment visit)/standard deviation) of 0.5 with a two-sided type I error of 0.05. Comparisons of demographic characteristics and baseline disease status between placebo and active device treatment groups and study sites were performed using Student's t-test and one way analysis of variance (ANOVA) for continuous variables and the Chi-square test and Cochrane-Mantel-Haenszel test for categorical variables. Use of concomitant arthritis medications (NSAIDs, DMARDs, corticosteroids, and analgesics), distributions of patient dropout, and adverse device effects were compared using the Chi-square test. Appropriate transformations were applied for continuous variables with skewed distribution. Scores for the outcome measures from the 2 baseline visits were averaged to derive a baseline score. Both raw scores and percent

improvement from baseline were determined for each of the weekly visits during which patients received treatment. Treatment effects were assessed using repeated measures models with either mixed linear models (for continuous outcomes) or generalized estimating equations (for binary outcomes). Covariance structure was selected using Akaike's Information Criterion to compensate for the dependency among the multiple observations from the same patient. An intent-to-treat analysis was conducted for all parameters. The clinical data were audited by C. L. McIntosh Associates, Inc. of Rockville, Maryland.

Results

Eighty-nine patients (45 active BioniCare devices and 44 placebo BioniCare devices) were enrolled from 6 study centers. Eleven patients (12%) did not complete the study, including 7 active patients and 4 placebo patients (not significantly different). Reasons for dropout included: 3 patients (all in the active group) withdrew because of unrelated health problems (1 each for knee flare, bronchitis, and diabetes); 3 patients (1 active, 2 placebo) withdrew because of rash; 2 (1 active, 1 placebo) withdrew because their arthritis medications had to be changed. One (active) withdrew because of a rash and flare in knee arthritis. One (placebo) discontinued because of inconvenience and lack of efficacy. One patient withdrew consent before receiving any treatment.

An intent-to-treat analysis demonstrated that the BioniCare stimulator is effective in providing statistically significant reduction in the signs and symptoms of RA of the hand, as measured by patient evaluation of function (P = .002) **(Figure 5)**, patient evaluation of pain and symptoms (P = .007) **(Figure 6)**, and the physician's global assessment (P = .022) **(Figure 7)**. The significant improvements for these clinical outcomes were observed in absolute improvement of the visual analog scale scores as well as in percent improvement. In addition, the BioniCare treatment was demonstrated to be safe, with transient skin rashes as the only adverse event. There was no statistically significant difference in skin rashes in the active BioniCare as compared to the placebo BioniCare devices, suggesting that they were the consequence of extended skin contact with the electrodes rather than the actual electrical stimulation.

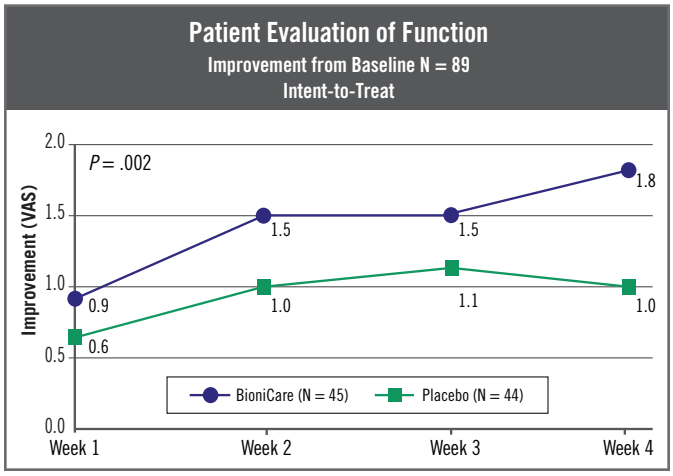

FIG. 5: Patient Evaluation of Function
Abbreviation: VAS, visual analog scale.

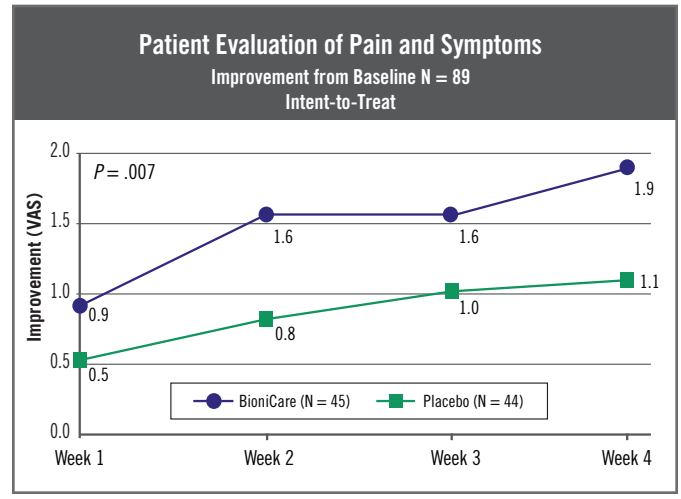

FIG. 6: Patient Evaluation of Pain and Symptoms
Abbreviation: VAS, visual analog scales.

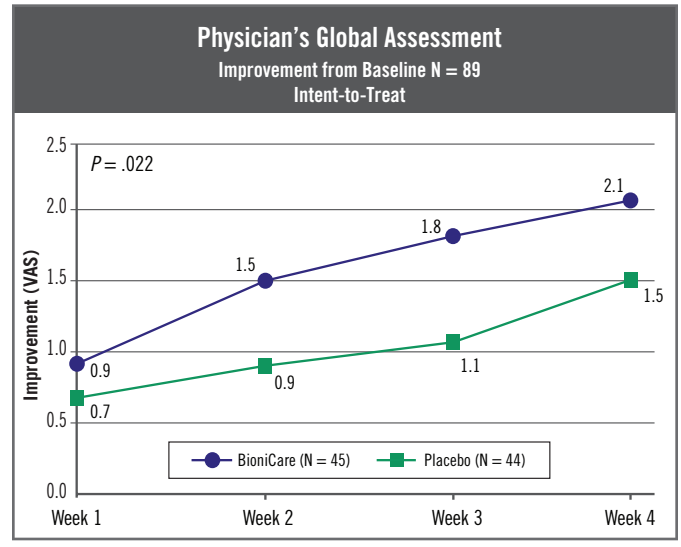

FIG. 7: Physician's Global Assessment
Abbreviation: VAS, visual analog scale.

Comment

This study was the basis for BioniCare's submission of an application for premarket approval (PMA). At that time, there were more than 400 PMA applications pending in the device section of the FDA. Six years later, 200 such applications were still pending. As a result of increasing pressure from Congress to clear the backlog, the FDA suggested that BioniCare withdraw its application for PMA and accept a 510(k) predicate clearance. Consequently, the BioniCare Hand System was cleared with an indication "for use as adjunctive therapy in reducing the level of pain and stiffness associated with pain from rheumatoid arthritis of the hand."

Osteoarthritis

The prevalence of symptomatic hand osteoarthritis (OA) in the Framingham subjects was 16% for women and 8% for men and was especially high in older adults.[19] Using the Framingham data on age/sex prevalence among persons aged ≥26 years and the corresponding 2005 population estimates from the Census Bureau, the National Arthritis Data Workgroup estimated that 9,267,000 adults have symptomatic knee OA and 13,054,000 adults have symptomatic hand OA.[20] Elderly women are more likely to have hand involvement compared with men. The most frequently affected joints are the distal interphalangeal (DIP), proximal interphalangeal (PIP), thumb interphalangeal, and trapeziometacarpal joints.[21] OA is characterized by degradation of cartilage, resulting in joint destruction and osteophyte formation.[22]

The development and progression of OA are now believed to involve inflammation, even in the early stages of the disease.[23] Epidemiological studies show a clear relationship between the progression of tibiofemoral cartilage damage and the presence of a reactive or inflammatory synovium.[24,25] Interleukin-1 beta (IL-1ß), TNF, and IL-6 seem to be the main proinflammatory cytokines involved in the pathophysiology of OA. IL-1ß seems to be associated with cartilage destruction and TNF with driving the inflammatory cascade. These 2 cytokines, which are produced by chondrocytes, mononuclear cells, osteoblasts, and synovial tissues, induce the production of a number of inflammatory and catabolic factors.[26] In patients with OA, levels of both IL-1ß and TNF are elevated in the synovial fluid, synovial membrane, subchondral bone, and cartilage. IL-1ß and TNF induce production of proinflammatory cytokines such as IL- 6 and chemokines such as IL-8, as well as stimulate the production of a number of other inflammatory mediators such as inducible nitric oxide synthase (iNOS), soluble phospholipase A2, cyclooxygenase two (Cox-2), nitric oxide (NO), and prostaglandin E2 (PGE2). NO and PGE2 contribute to articular inflammation and destruction by enhancing the activation and production of the matrix metalloproteinases (MMPs), inhibiting the synthesis of anabolic macromolecules such as collagen and proteoglycan, and promoting chondrocyte apoptosis.[26]

Thumb carpometacarpal joint OA in the trapeziometacarpal joint is particularly common in perimenopausal women. Patients often complain of some weakness because of pain. Examination may reveal a positive grind test, which is axial compression of the joint causing pain from the denuded articular surfaces rubbing against each other. The initial treatment may consist of splinting or steroid injections into the joint. Clinical trials examining the efficacy of therapeutic approaches to OA of the hand, specifically, are limited.[27-29] Management of hand OA has been largely derived from the knowledge obtained in treatment of OA in other joints.[30]

For patients with sufficient joint destruction, surgical treatment may consist of trapeziectomy augmented by adjuvant procedures including ligament reconstruction and tendon interposition, abductor pollicus longus suspensionplasty, trapeziometacarpal joint replacement, or carpometacarpal arthrodesis. Treatment of the proximal interphalangeal joints of the digits in the OA hand is dependent on location. In general, the radial digits tend to be treated with arthrodesis to provide a strong post for pinch. By contrast, the ulnar digits require motion and tend to be treated with an implant arthroplasty. Appropriate use of arthroplasty and arthrodesis for the affected joints requires careful consideration of the patient's needs for the affected digits.

Interest in using the BioniCare Hand System for OA of the hand and wrist is due to the efficacy of the BioniCare device in knee OA. This has been examined extensively in the past 20 years with 5 studies involving 104 clinical settings and 907 patients. Two, short-term, double blind, randomized, multicenter clinical trials comparing the BioniCare device to a placebo device provided level 1 evidence for its effectiveness.[31,32] Three long-term clinical studies were then conducted to determine changes in the disease state and safety of the BioniCare device, and these also demonstrated statistically significant clinical effectiveness.[33-35] Because of the successful experience in OA of the knee and the successful placebo-device controlled randomized clinical trial in RA of the hand, a prospective, multicenter study to determine the safety and efficacy of the BioniCare system for treating OA of the hand was launched in 2012.

Material and Methods

The study is designed as a 4-month, multicenter, prospective study. Inclusion criteria required patients who were aged 18 years or older; with a clinical diagnosis of OA of the hand for at least 3 months prior to study entry; a score of 3 or greater on a 10 point Likert Scale for "Pain in the past 48 hours" in the treated hand; analgesics and/NSAIDs must have been stable for 30 days prior to entry; and patients must be willing to wear the BioniCare Hand Device for at least 6 hours per day. Most of the patients used the device while sleeping. Exclusion criteria were: women who are pregnant, breast-feeding, or who are planning to become pregnant; infectious arthritis, including, but not limited to, tuberculosis, post-Lyme disease, etc; patients with infections in the treated hand in the previous 6 months; patients with pacemakers or any implanted devices; patients with the diagnosis of gout, recurrent, inflammatory episodes of pseudogout, malignancy, inflammatory arthritis, such as RA, psoriatic arthritis, Reiter's syndrome, ankylosing spondylitis, or collagen vascular diseases; history of malignancy within the past 3 years; history of drug or alcohol abuse within

the past 2 years; intellectual or psychological inability to complete the patient questionnaires; patients involved in litigation or receiving Workmen's Compensation; patients who participated in any investigational study within the previous month; and patients with surgery in the treated/study hand in the previous 6 months. Efficacy outcomes consisted of OA pain in the study hand over the past 48 hours, OA pain in the study thumb in the past 48 hours, the patient global assessment, physician's global assessment, pinch force, grip strength, and the DASH (Disabilities of the Arm, Shoulder and Hand) functional questionnaire results. Outcomes utilized in the treatment of hand disorders are difficult to assess because the major areas of interest are improvement in quality of life and function, variables that are hard to quantify. Because of this the DASH was jointly developed by the Institute for Work and Health and the American Academy of Orthopedic Surgeons (AAOS).[36] The DASH outcome measure is a 30-item, self-report questionnaire designed to measure physical function and symptoms in people with any of several musculoskeletal disorders of the upper limb. The tool gives clinicians and researchers the advantage of having a single, reliable instrument that can be used to assess any or all joints in the upper extremity. All sites were provided with the JAMAR Hand Assessment Kit which includes a squeeze (grip) dynamometer and a pinch dynamometer. The sites were instructed in use of the dynamometers and the procedure for obtaining the measurements. Pinch force and grip strength were determined by taking the average of three successive efforts with the patient in a seated position.

EFFECT SIZES OF BIONICARE FOR OA OF THE HAND

N = 82	OA PAIN IN STUDY HAND PAST 48 HOURS		OA PAIN IN STUDY THUMB PAST 48 HOURS		SUBJECT GLOBAL ASSESSMENT OA STUDY HAND		PATIENT DASH QUESTIONNAIRE		HAND ASSESSMENT PINCH FORCE	HAND ASSESSMENT GRIP STRENGTH	PHYSICIAN'S GLOBAL ASSESSMENT OA STUDY HAND
Week Number	0	4	0	4	0	4	0	4			
Mean	5.4	3.6	4.7	3.1	5.4	3.6	38.1	32.9			
SD	1.4	1.9	2	2.1	1.5	2	15.8	17.3	ND	ND	ND
	1.6		2.1		1.8		16.6				
Size Effect	1.1		0.8		1		0.3				

N = 66	OA PAIN IN STUDY HAND PAST 48 HOURS		OA PAIN IN STUDY THUMB PAST 48 HOURS		SUBJECT GLOBAL ASSESSMENT OA STUDY HAND		PATIENT DASH QUESTIONNAIRE		HAND ASSESSMENT PINCH FORCE		HAND ASSESSMENT GRIP STRENGTH		PHYSICIAN'S GLOBAL ASSESSMENT OA STUDY HAND	
Week Number	0	8	0	8	0	8	0	8	0	8	0	8	0	8
Mean	5.5	3.3	4.7	3.1	5.5	3.4	37.7	30.4	4.8	5.7	19.6	22.4	5.9	4
SD	1.4	2	1.9	2.2	1.4	2	15.9	15.3	2.2	2.2	8.8	9	1.5	1.9
	1.7		2.1		1.7		15.6		2.2		8.9		1.7	
Size Effect	1.3		0.8		1.2		0.5		0.4		0.3		1.1	

TABLE 1: Effect Sizes of BioniCare for OA of the Hand
Abbreviations: ND, not done per protocol; OA, osteoarthritis; SD, standard deviation.

Statistical Analysis

When both hands were affected, the more symptomatic one was designated as the index hand to be followed. Statistical Analysis System (SAS) software version 9.1.3 was used. Univariate "screening" of associations between covariates and outcomes were done by simple statistical method-tests, Chi-square, and log-rank tests. Selected covariates were examined in the Cox model. Patient baseline values served as controls for post-treatment values. Differences between baseline and final visit scores were compared using paired samples t-tests. A multivariate analysis examined the effects of age, gender, and number of hours of device usage on efficacy. Efficacy was expressed for each variable as the effect size. Effect sizes were previously defined by a 2003 EULAR task force as small from 0.2 to 0.5; moderate from 0.5 to 1.0; and large as greater than 1.0.[37] By protocol, an interim analysis was projected after 2 months of treatment with the BioniCare Hand System and final analysis will be completed after 4 months of treatment.

Results

The first 82 patients with OA of the hand have completed the initial 1 month of treatment. There were 66 females and 16 males who ranged in age from 45 to 89 years with a mean age of 64 years. In the intent-to-treat analysis the effect size for OA pain in the study hand in the past 48 hours was 1.1, for OA pain in the study thumb in the past 48 hours was 0.8, for the patient global assessment of the OA study hand was 1.0, and for the DASH functional questionnaire was 0.3 (**Table 1**). At the point of the interim analysis, 66 patients had completed 8 weeks of treatment. The intent-to-treat analysis demonstrated that large effect sizes were present for OA pain in the study hand in the past 48 hours (1.3), patient global assessment (1.2), and physician's global assessment (1.1). Medium effect sizes were seen for OA pain in the study thumb in the past 48 hours (0.8) and the DASH functional questionnaire (0.5). Smaller but still significant effect sizes were seen for the objective measurements of pinch force (0.4) and hand grip strength (0.3) (**Table 1**).

Comment

It is impressive that all of the outcome measures were significantly improved including the more objective measures such as physician's global assessment, the DASH functional questionnaire, pinch force, and grip strength. It should be noted that rarely are these objective functional tests improved with surgery. For example, in a prospective outcomes study of MCP joint arthroplasty it was found that pain did decrease significantly 6 months and 1 year after surgery ($P < .01$). Functional tests such as grip and pinch strength, however, improved only minimally 1 year after surgery.[38] Other studies also have found that when comparing postoperative values with preoperative values, there usually is no significant improvement in objective measures such as grip strength.[39-41]

Carpal Tunnel Syndrome

The carpal tunnel is formed by the transverse carpal ligament (flexor retinaculum) superiorly with the carpal bones inferiorly. The nine flexor tendons of the forearm musculature and the median nerve pass through this anatomic tunnel. When compression of the median nerve occurs, it causes ischemia and mechanical disruption of the nerve. Carpal tunnel syndrome (CTS) refers to the complex of symptoms and signs brought on by compression of the median nerve as it travels through the carpal tunnel. Patients commonly experience pain, paresthesia, and less commonly, weakness in the median nerve distribution. CTS is one of the most common peripheral nerve disorders with population prevalence of 5.8% in women and 0.6% in men.[42] CTS and hearing loss was found to account for more morbidity, measured by cases and working days lost, than any other illness in the US working population.[43]

While the precise etiology of increased carpal tunnel pressure in idiopathic CTS is uncertain, experimental evidence suggests that anatomic compression and/or inflammation are possible mechanisms. The role of overuse of the hand, particularly light repetitive work, in causation of CTS has not been definitely established; however, one interesting study showed enlargement, and T2 signal change on magnetic resonance imaging of the median nerve 8 hours after a 3-hour period of typing in healthy office workers.[44] Inflammatory and proinflammatory cytokines have been shown to be elevated in the flexor tenosynovium of idiopathic CTS.[45-47] Injection of glucocorticoids in the region of the carpal tunnel is intended to reduce the inflammation and aids recovery. In general, glucocorticoid injections appear effecive in reducing subjective symptoms of CTS for 1 to 3 months when compared with placebo.[48-50] The "definitive" procedure of surgical decompression is by no means uniformly successful. Pooling the reported results of 207 published surgical series between 1956 and 2005 reveals an overall success rate for surgical treatment of 75% in 32,761 cases and there is an overall trend for more recently published series to report lower success rates.[51] The average time to return to work after surgery is almost a month and a recent study showed 22% of patients were out of work 12 months after carpal tunnel decompression.[52] These facts plus the demonstration that the BioniCare Hand System was efficacious in RA of the hand, an inflammatory condition, led to the trial of the BioniCare Hand System for the treatment of CTS.

Materials and Methods

The study is designed as a 4-month, multicenter, prospective study. Inclusion criteria required patients who were 18 years or older; with a clinical diagnosis of CTS for at least 3 months prior to study entry; a score of 3 or greater on a 10 point Likert Scale for "Pain in the past 48 hours" in the treated hand; analgesics and/NSAIDs must have been stable for 30 days prior to entry; and patients must be willing to wear the BioniCare Hand Device for at least 6 hours per day. Most of the patients used the device while sleeping. Exclusion criteria were: women who are pregnant, breast-feeding, or who are planning to become pregnant; infectious arthritis, including, but not limited to, tuberculosis, post-Lyme disease, etc; patients with infections in the treated hand in the previous 6 months; patients with pacemakers or any implanted devices; patients with the diagnosis of gout, recurrent, inflammatory episodes of pseudogout, malignancy, inflammatory arthritis, such as RA, psoriatic arthritis, Reiter's syndrome, ankylosing spondylitis or collagen vascular diseases; history of malignancy within the past 3 years; history of drug or alcohol abuse within the past 2 years; intellectual or psychological inability to complete the patient questionnaires; patients involved in litigation or receiving Workmen's Compensation; patients who participated in any investigational study within the previous month; and patients with surgery in the treated/study hand in the previous 6 months.

Efficacy outcomes consisted of carpal tunnel pain in the study hand on the day of evaluation, carpal tunnel paresthesias on the day of evaluation, weakness due to CTS on the day of evalution, global carpal tunnel symptoms over the past 48 hours, physician's global assessment, pinch force, grip strength, and the DASH (Disabilities of the Arm, Shoulder and Hand) functional questionnaire results. Outcomes utilized in the treatment of hand disorders are difficult to assess because the major areas of interest are improvement in quality of life and function, variables that are hard to quantify. Because of this the DASH was jointly developed by the Institute for Work and Health and the American Academy of Orthopedic Surgeons (AAOS).[36] The DASH outcome measure is a 30-item, self-report questionnaire designed to measure physical function and symptoms in people with any of several musculoskeletal disorders of the upper limb. The tool gives clinicians and researchers the advantage of having a single, reliable instrument that can be used to assess any or all joints in the upper extremity. All sites were provided with the JAMAR Hand Assessment Kit which includes a squeeze (grip) dynamometer and a pinch dynamometer. The sites were instructed in use of the dynamometers and the procedure for obtaining the measurements. Pinch force and grip strength were determined by taking the average of three successive efforts with the patient in a seated position.

Statistical Analysis

When both hands were affected, the more symptomatic one was designated as the index hand to be followed. Statisti-

EFFECT SIZES OF BIONICARE FOR CARPAL TUNNEL SYNDROME																
N = 16	CTS PAIN PAST 48 HOURS		CTS PARESTHESIA PAST 48 HOURS		WEAKNESS DUE TO CTS PAST 48 HOURS		ALL CTS SYMPTOMS PAST 48 HOURS		PATIENT DASH QUESTIONNAIRE		HAND ASSESSMENT PINCH FORCE		HAND ASSESSMENT GRIP STRENGTH		PHYSICIAN'S GLOBAL ASSESSMENT	
Week Number	0	4	0	4	0	4	0	4	0	4						
Mean	4.4	3.6	3.8	2.8	4.4	3.6	4.6	3.6	49.1	43.5						
SD	2	2.6	2.3	2.4	2.2	2.4	2	2.2	17.8	20	ND		ND		ND	
	2.3		2.4		2.3		2.1		18.9							
Size Effect	0.4		0.4		0.4		0.5		0.3							
N = 14	CTS PAIN PAST 48 HOURS		CTS PARESTHESIA PAST 48 HOURS		WEAKNESS DUE TO CTS PAST 48 HOURS		ALL CTS SYMPTOMS PAST 48 HOURS		PATIENT DASH QUESTIONNAIRE		HAND ASSESSMENT PINCH FORCE		HAND ASSESSMENT GRIP STRENGTH		PHYSICIAN'S GLOBAL ASSESSMENT	
Week Number	0	8	0	8	0	8	0	8	0	8	0	8	0	8	0	8
Mean	4.7	2.8	4	2.8	4.4	3.1	4.8	3.1	50	38.9	5.2	5.6	18.3	20.2	4.3	3.7
SD	1.8	2.1	2.3	2.1	2	2	1.8	1.8	15.1	17.6	1.9	2.7	8.6	9.8	1.8	2.3
	1.9		2.2		2		1.8		16.3		2.3		9.2		2	
Size Effect	1.3		1.4		0.5		1.4		0.9		0.1		0.2		0.2	

TABLE 2: Effect Sizes of BioniCare for Carpal Tunnel Syndrome
Abbreviations: CTS, carpal tunnel syndrome; ND, not done per protocol; SD, standard deviation.

cal Analysis System (SAS) software version 9.1.3 was used. Univariate "screening" of associations between covariates and outcomes were done by simple statistical method-tests, Chi-square, and log-rank tests. Selected covariates were examined in the Cox model. Patient baseline values served as controls for post-treatment values. Differences between baseline and final visit scores were compared using paired samples t-tests. A multivariate analysis examined the effects of age, gender, and number of hours of device usage on efficacy. Efficacy was expressed for each variable as the effect size. Effect sizes were previously defined by a 2003 EULAR task force as small from 0.2 to 0.5; moderate from 0.5 to 1.0; and large as greater than 1.0.[37] By protocol, an interim analysis was projected after 2 months of treatment with the BioniCare Hand System and final analysis will be completed after 4 months of treatment.

Results

Sixteen patients with OA of the hand also had symptomatic CTS. They were treated with the BioniCare hand system for 6 or more hours per day, usually while they slept at night. The outcome measures at 4 weeks were: CTS pain in the past 48 hours, paresthesias in the past 48 hours due to CTS, weakness in the past 48 hours due to CTS, all CTS symptoms in the past 48 hours, and the DASH functional questionnaire, and at 8 weeks, were the same parameters with the addition of grip strength, pinch force, and the physician's global assessment of CTS. At 4 weeks, the intent-to-treat analysis demonstrated an effect size for CTS pain in the past 48 hours of 0.4, for paresthesias in the past 48 hours due to CTS it was 0.4, for weakness in the past 48 hours due to CTS it was 0.4, for all CTS symptoms in the past 48 hours it was 0.5, and for the DASH functional questionnaire it was 0.3 (**Table 2**).

Fourteen of these patients were evaluated at 8 weeks. The effect size for CTS pain in the past 48 hours was 1.3, for paresthesias in the past 48 hours due to CTS it was 1.4, for weakness in the past 48 hours due to CTS it was 0.5, for all CTS symptoms in the past 48 hours it was 1.4, for the DASH functional questionnaire it was 0.9, for pinch force it was 0.1, for grip strength it was 0.2, and for the physician's global assessment of CTS it was 0.2.

Comment

Although the manifestations of CTS required more treatment time to improve, such that outcome measures had only small to moderate effect sizes at 4 weeks, there was substantial improvement by 8 weeks such that CTS pain, CTS paresthesias, and global CTS symptoms in the past 48 hours, all had large effect sizes after 8 weeks of treatment.

SUMMARY

In summary, it has been demonstrated that the BioniCare Hand System is effective in providing clinically relevant and statistically significant reduction in the signs and symptoms of RA of the hand. Based on numerous studies and successful experience in OA of the knee, and significant improvement in all 7 outcome parameters in the OA of the hand study, the BioniCare Hand System will be a welcome addition to the armamentarium for OA of the hand and wrist. In the interim analysis reported herein, all 7 outcomes parameters were improved including the more objective measures such as pinch force, grip strength, the DASH functional questionnaire, and the physician's global assessment. A subset of the OA of the hand patients had CTS, which similarly benefited, particularly after 8 weeks of treatment with the BioniCare Hand System.

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