Summary of a Randomized, Double-Blinded, Comparative Crossover Trial of the Safety and Efficacy of a Non-Invasive Targeted Electronic Pain Control Device ("Biowave System") *Versus* Transcutaneous Electrical Nerve Stimulation (TENS) for the Symptomatic Treatment of Chronic Low Back Pain; March 2006

Location: **Weill Medical College of Cornell University**
New York Presbyterian Hospital
New York, NY

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Introduction

The Biowave System (Biowave Corporation, Norwalk, CT) introduces two summed alternating current high frequency sine waves into the body through a first disposable non-invasive round electrode (2 inches in diameter) placed on the skin directly over the pain site. Polarized structures inside the body including nociceptive pain fibers cause the two summed high frequency signals to multiply together forming a new spectrum of signals in a 3-inch diameter hemisphere beneath the first electrode. The multiplication of the two sine waves is known as a Fourier Transform. One of the signals formed resulting from the multiplication is a low frequency signal in the form of an active electrical field that is optimized for hyperpolarizing C-fibers and inducing hypoesthesia on A-delta fibers that fall within the 3-inch diameter hemisphere inside the body. Because the device is an alternating current device, instantaneously the device alternates the delivery of the summed high frequency signals to the second electrode. The active electrical field forms in a hemisphere beneath the second electrode. The device alternates the delivery of the summed high frequency signals back and forth so quickly between the two electrodes, that the patient cannot distinguish that the signals have left either location. The net effect is there are two active electrodes, each of which can treat a distinct volume of tissue simultaneously and there is no noxious twitching sensation.

The use of different sized electrodes concentrates the electric field in the volume of tissue surrounding and beneath the smaller round electrode which must be placed over the location of pain. The sensation felt by the patient is a comfortable pressure and tingling sensation without muscle twitching or the noxious sensation that is common with other electrotherapy devices. This technology is being explored as a novel therapy for treating chronic, acute or post-surgical pain in the low back, shoulder, neck, hip, knee, elbow, face, legs, arms, wrist, hands, ankles and feet.

Methods

The IRB approved study was a double blinded, randomized, controlled crossover trial for the treatment of chronic low back pain. The study was conducted at Weill Medical College of Cornell University/New York Presbyterian Hospital in New York City. The purpose of the study was to show that (1) the Biowave System has superior efficacy over an active control, specifically a TENS (Transcutaneous Electrical Nerve Stimulation) device for the treatment of chronic low back pain, and (2) that the Biowave System provides a much longer residual period of pain relief than TENS following a 20-minute duration treatment.

In order to be eligible for the study, patients had to record a baseline pain measurement of 40 mm or higher on a visual analog scale (VAS) that was 100 mm in length. Once a patient was enrolled they were exposed to both devices through the use of a crossover design. The order of

the devices to which each patient was exposed, was randomly determined before the study began.

36 treatments were performed on 18 patients. Each patient received one treatment on each device. The treatments were separated by one week to ensure a proper washout period between the two devices. The patients were blinded from the devices by having the devices concealed within a large carton. There were two investigators: the investigator interviewing the patient and collecting initial patient data was also blinded from which device was being used; the second investigator was responsible for controlling the intensity of the device. For each treatment, the leadwires and electrodes were identical in appearance: 3 leadwires emanated from the carton and 3 electrodes were placed on the patient. One large 8" x 5" dispersive electrode was placed on the abdomen, and two smaller 2-inch diameter round electrodes were placed bilaterally on the lower back. For the Biowave treatment, only one of the small round electrodes on the lower back and the dispersive electrode on the abdomen were active. For the TENS device, only the two round electrodes on the lower back were active.

Before being exposed to each device, the patient recorded the level of both their surface back pain and their deep back pain on the visual analog scale (VAS). The patient's range of motion (ROM) was also assessed at baseline according to the protocol description. Each patient was then exposed to the first device for 20 minutes. Subsequently, the patient recorded their level of surface pain and deep pain at 0, 30, and 60 minutes following treatment, and in addition, at 4, 6, 12 and 24 hours following treatment. The patient's ROM was also re-assessed at 0, 30, and 60 minutes following treatment. A period of at least one week was allowed to pass before each patient was exposed to the second device.

Results

Nine patients were exposed to TENS first and Biowave second, while nine patients were exposed to Biowave first and TENS second.

Attached are table and charts with data from the study summarizing the results for the 18 patients. Patients completed two sets of Pain Visual Analog Scale (Pain VAS) scores for baseline and post treatment pain scores. One set is for evaluating "Surface Pain" and one set is for "Deep Pain". The tables and charts show data for average percent reduction in VAS pain scores at different points in time from baseline (pre-treatment) to 24 hours post treatment for both surface and deep pain.

The data shows not only that the Biowave System is more efficacious, but also that it has a substantially longer residual carryover effect when compared against TENS. This is true for the analyses shown in each chart.

The specific results in Table 1 and Figure 1 showed that the average percent reduction in surface pain for the Biowave System across all 18 patients was 82% at 1 hour, 82% at 6 hours and 73% at 24 hours post treatment, versus 63% at 1 hour, 63% at 6 hours and 36% at 24 hours for TENS. In Table 2 and Figure 2, for deep pain, the average percent reduction in pain for the Biowave System across all 18 patients was 75% at 1 hour and 53% at 24 hours post treatment versus 63% at 1 hour and 37% at 24 hours for TENS.

The controlled, crossover, randomized, double blinded results show that for the treatment of chronic low back pain, the Biowave System has as much as a 24%

improvement over TENS at one hour post treatment, and as much as a 51% improvement over TENS at 24 hours post treatment.

It should be noted that from the evaluation of both surface pain and deep pain, that for the Biowave System, patients' pain relief *improved* over the first 1 to 4 hours post treatment, as compared to TENS, where the level of patients' pain relief exhibited an immediate decline post-treatment.

Biowave appears to be an effective treatment for chronic low back pain and significantly better than TENS.

Discussion Regarding Flawed Study Design

1. **VAS Pain Measurements**

   For future studies, because patients had difficulty differentiating between "deep pain" and "surface pain," that only "pain" would be assessed using VAS measurements.

2. **Treatment Duration**

   Subsequently it has been determined that a 30-minute duration Biowave treatment provides a greater magnitude of pain relief and longer lasting residual benefit than a 20-minute treatment. Therefore future studies will include 30-minute duration Biowave treatments instead of 20-minute duration Biowave treatments. Had this study included a 30-minute duration treatment in its design, Biowave would have provided even better results over TENS than those captured in this study.

3. **Incorrect Electrode Size and Placement**

   Subsequently, it was discovered that the electrode placement design used in this study was flawed. It was originally thought that the Biowave electrodes needed to be in an opposing position to one another, hence one electrode on the abdomen and one over the pain site on the lumbar area of the back. Since the electrode placed on the abdomen is active and stimulation received over the abdomen is uncomfortable, patients complained that they couldn't increase the signal intensity to a high enough level for the pain site electrode on the back because the stimulation sensation felt on the abdomen prevented them from going higher.

   If the Biowave electrode placement used two same sized independent electrodes to treat two locations of pain on the lower back, patients would have been able to increase the intensity to a much higher level which would have provided greater and longer lasting pain relief. Patients can tolerate a much higher intensity setting over the lumbar back than anywhere on the anterior of the torso. In future low back pain studies, the Biowave treatment will use two independent same sized electrodes over two locations of pain or over the origin of pain and the most proximal location of pain to the origin on the lumbar area of the back. Had this study included the proper electrode size and placement in its design, Biowave would have provided significantly better results over TENS than those captured in this study.

Biowave Corporation
Confidential Test Results - Phase 3
Cornell Blinded Controlled Randomized Crossover Chronic Low Back Pain Study
Comparing Biowave vs. TENS
n=18 Patients

SURFACE PAIN
AVG % REDUCTION in VAS

Time (Hrs)	Biowave	TENS	Biowave Imrpovement Over TENS
0	74%	68%	8%
0.5	82%	62%	24%
1	82%	63%	24%
4	83%	65%	21%
6	82%	63%	23%
12	77%	58%	25%
24	73%	36%	51%

Table 1

DEEP PAIN
AVG % REDUCTION in VAS

Time (Hrs)	Biowave	TENS	Biowave Imrpovement Over TENS
0	62%	66%	-6%
0.5	69%	57%	18%
1	75%	63%	17%
4	69%	61%	12%
6	67%	58%	13%
12	56%	51%	11%
24	53%	37%	31%

Table 2

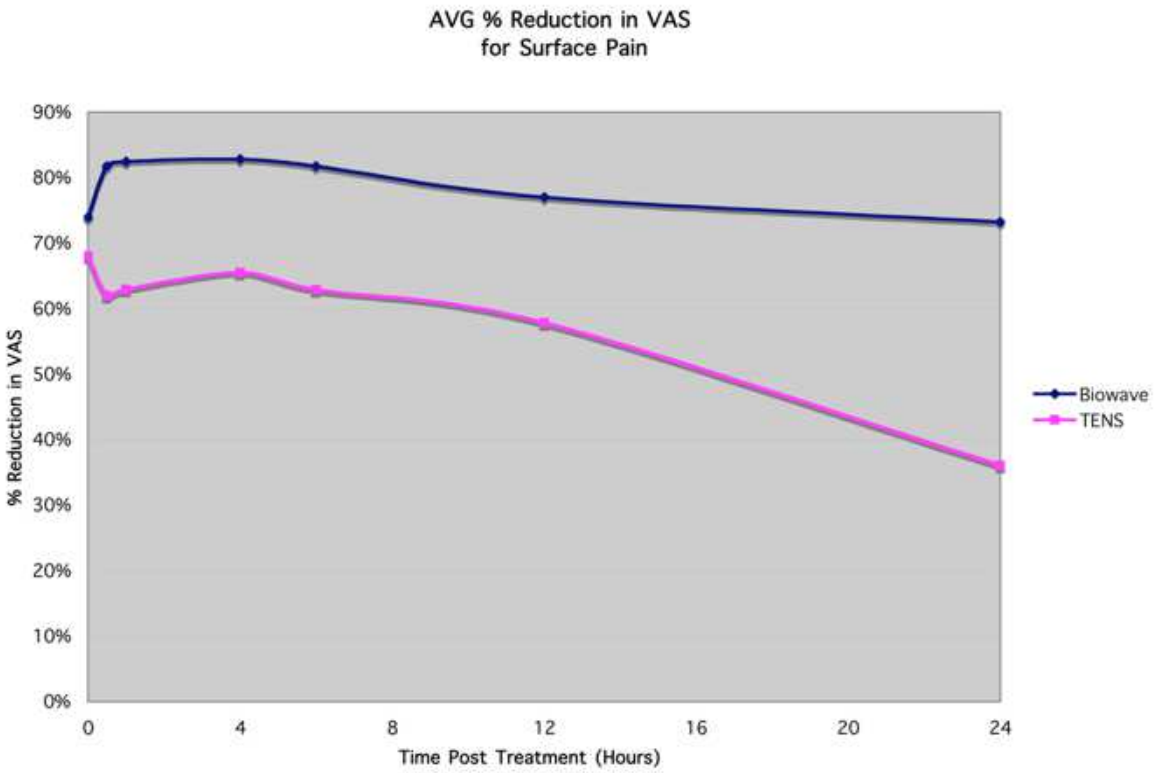

Figure 1. Average Percent Reduction in VAS for Surface Pain-
Cornell Double Blinded Controlled Randomized Crossover Chronic Low Back Pain Study

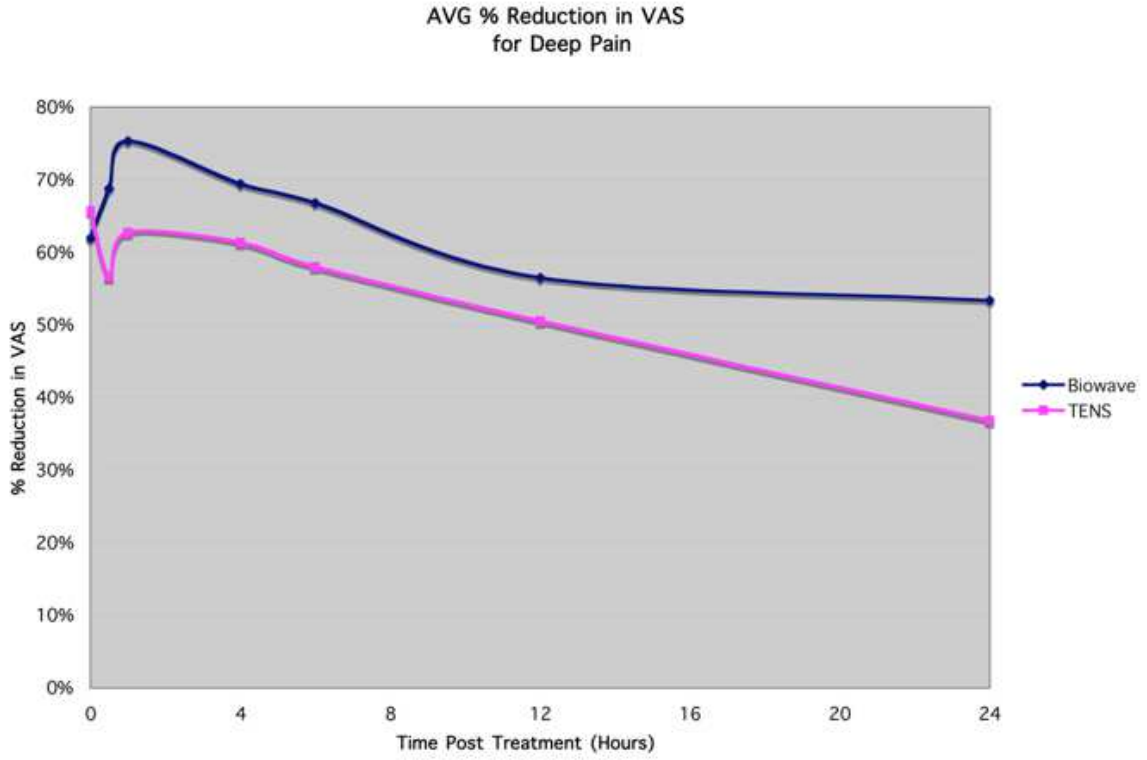

Figure 2. Average Percent Reduction in VAS for Deep Pain
Cornell Double Blinded Controlled Randomized Crossover Chronic Low Back Pain Study