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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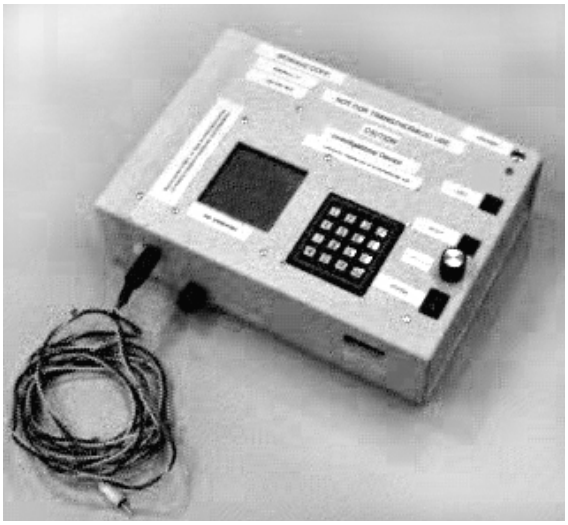
1. Introduction

Low back pain is a common, costly and often chronic condition, estimated to affect up to 85% of people in their lifetime. The direct medical costs and indirect costs, including disability and lost wages, of low back disorders are estimated at $50 - $100 billion per year. Current treatments are less than ideal: commonly used opioid and non-opioid analgesic drugs produce adverse effects, while many non-pharmacologic therapies are invasive or of questionable therapeutic value. New therapies for the effective management of chronic back pain are clearly needed.

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 Biowave 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.

2. Biowave Device



The prototype device measures 7.87 inches wide, 11 inches long, and 3 inches deep, weighs about 3.75 pounds, and operates on two 6-volt rechargeable batteries which are enclosed within the unit. The unit will not operate while it is plugged into the wall to recharge the batteries. The patient controls the amplitude of the signal with two buttons (an UP arrow, and a DOWN arrow) on a keypad on the face of the device. An LCD displays the amplitude of the signal in a bar graph and numerical format. Two wires emanate from the unit. One wire is attached to a large dispersive electrode ("Feed Electrode") placed opposite the pain site. The second wire is attached to a smaller round electrode ("Pain Site Electrode") placed over the location of pain (the treatment site).

3. 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 in the study, 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. The advantage of a crossover design is that the comparison of Biowave vs TENS is conducted on the same patient, for all patients participating in the study, which provides greater statistical significance for a given treatment group size.

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 on the lower back directly over locations of pain. For the Biowave treatment, only one of the small round electrodes on the lower back and the dispersive electrode on the abdomen were active and the active smaller round electrode was placed directly over the location of pain in the lumbar area including over the lumbar spine. For the TENS device, only the two round electrodes on the lower back were active and the two electrodes were placed bilaterally surrounding the pain site.

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.

4. Results

The data shows that the Biowave System is safe, provides significantly better and longer lasting pain relief than TENS, and that the Biowave System provides pain relief for up to 24 hours for patients suffering from chronic low back pain.

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

There were no adverse events amongst any patients in both of the treatment groups.

Below are tables 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 "Deep Pain" and one set is for "Surface 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 Deep and Surface 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 the charts for both Deep Pain and Surface Pain.

4.1 Deep Pain

The results in Table 1 and Figure 1 show that the average percent reduction in VAS pain scores for deep pain for the Biowave System across all 18 patients was a 75.3% reduction in pain at 1 hour post treatment and 53.4% reduction in pain at 24 hours post treatment, versus 62.7% at 1 hour and 36.8% at 24 hours for TENS.

Table 1

DEEP PAIN AVG % REDUCTION in VAS (n=18 patients)			
Time (Hrs)	Biowave	TENS	Biowave Improvement over TENS
0	61.9%	65.7%	-6.2%
0.5	68.8%	56.6%	17.7%
1	75.3%	62.7%	16.8%
4	69.4%	61.4%	11.6%
6	66.8%	58.0%	13.2%
12	56.5%	50.5%	10.6%
24	53.4%	36.8%	31.1%

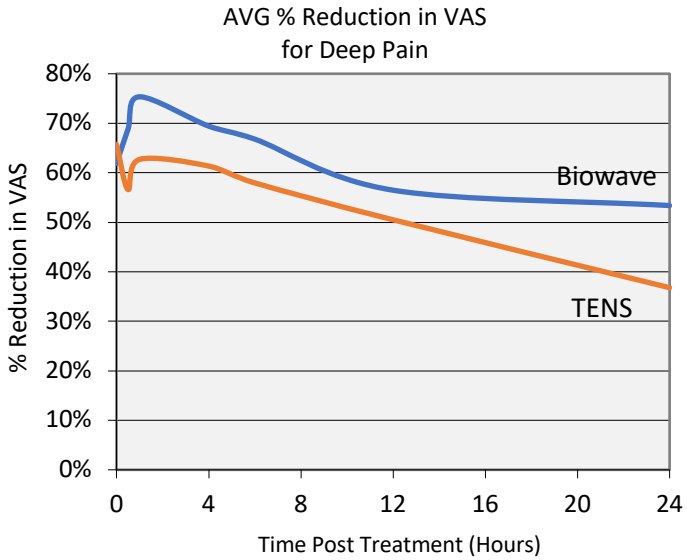


Figure 1. Average Percent Reduction in VAS for Surface Pain- Cornell Double Blinded Controlled Randomized Crossover Chronic Low Back Pain Study

4.2 Surface Pain

The results in Table 2 and Figure 2 show that the average percent reduction in VAS pain scores for surface pain for the Biowave System across all 18 patients was an 82.4% reduction in pain at 1 hour post treatment, 81.8% reduction in pain at 6 hours post treatment and 73.2% reduction in pain at 24 hours post treatment, versus 62.9% at 1 hour, 62.8% at 6 hours and 36.1% at 24 hours for TENS.

Table 2

SURFACE PAIN AVG % REDUCTION in VAS (n=18 patients)			
Time (Hrs)	Biowave	TENS	Biowave Improvement over TENS
0	73.9%	68.0%	8.1%
0.5	81.7%	62.0%	24.2%
1	82.4%	62.9%	23.7%
4	82.8%	65.5%	20.9%
6	81.8%	62.8%	23.1%
12	77.0%	57.8%	24.9%
24	73.2%	36.1%	50.7%

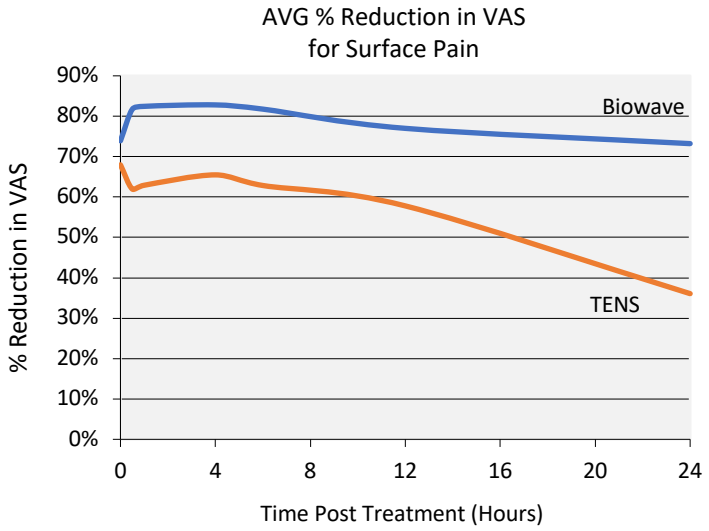


Figure 2. Average Percent Reduction in VAS for Deep Pain Cornell Double Blinded Controlled Randomized Crossover Chronic Low Back Pain Study

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 23.7% improvement over TENS at one hour post treatment, and as much as a 50.7% improvement in magnitude of pain relief over TENS at 24 hours post treatment.

4.3 Deep Pain vs Surface Pain

The results of the study show that within each treatment arm there is a small difference in the average percentage reduction in VAS pain scores between the evaluation of Deep Pain vs Surface Pain for the same device at the same time interval post treatment. It was noted during the study that the majority of patients had a very difficult time differentiating between "Deep Pain" and "Surface Pain." As a result, a second analysis was performed by averaging each patients' Deep Pain and Surface Pain VAS scores at each time interval.

Table 3

AVG % REDUCTION in VAS (n=18 patients/36 treatments)			
Time (Hrs)	Biowave	TENS	Biowave Improvement over TENS
0	63.6%	70.4%	-10.7%
0.5	67.6%	64.4%	4.6%
1	69.6%	67.0%	3.8%
4	74.1%	62.8%	15.2%
6	72.6%	59.6%	17.9%
12	65.7%	51.5%	21.6%
24	62.6%	35.0%	44.2%

In this analysis shown in Table 3 we analyze the average Deep and Surface Pain VAS scores for each patient for both Biowave and TENS treatments at each time interval post treatment. The average percent reduction in VAS pain scores for the Biowave System across all 18 patients was an 69.6% reduction in pain at 1 hour post treatment, 74.1% reduction in pain at 4 hours post treatment and 62.6% reduction in pain at 24 hours post treatment, versus 64.4% at 1 hour, 62.8% at 4 hours and 35.0% at 24 hours for TENS.

Biowave treatments provide increasing pain relief over the first 4 hours as compared to TENS where pain relief drops immediately post treatment and at 24 hours post treatment Biowave has a 44.2% improvement in magnitude of pain relief over TENS.

4,4 Duration of Pain Relief Post Treatment

The duration of pain relief 24 hours post treatment for both Deep Pain and Surface Pain was significantly better for patients when treated with the Biowave System then when treated with TENS.

4.4.1 Deep Pain

As shown in Figure 1, for Deep Pain, in the Biowave treatment arm, patients' pain relief *improved* over the first 1 to 2 hours post treatment, as compared to the TENS arm, where the level of patients' pain relief exhibited an immediate decline post-treatment. The magnitude of pain relief was better for patients treated in the Biowave treatment arm as compared to the TENS treatment arm for each time period measured starting at 30 minutes post treatment to 24 hours post treatment.

At 24 hours post treatment the Biowave System had a 31.1% improvement in magnitude of pain relief over TENS.

4.4.2 Surface Pain

As shown in Figure 2, for Surface Pain, in the Biowave treatment arm, patients' pain relief *improved* over the first 4 hours post treatment, as compared to TENS, where the level of patients' pain relief exhibited an immediate decline post-treatment. The magnitude of pain relief was better for patients treated with Biowave as compared to TENS at each time measured from immediately post treatment to 24 hours post treatment.

At 24 hours post treatment the Biowave System had a 50.7% improvement in magnitude of pain relief over TENS.

4.5 Percentage of Patients that Experienced Significant Pain Relief

Results show that more than 80% of patients receive significant pain relief over a 24 hour period post treatment.

Reduction in VAS Pain Scores of at least 30% is generally considered by pain health care providers to be a significant reduction in pain which more than accounts for potential placebo effects.

As shown in Table 4, when patients received a Biowave treatment, at 1 hour post treatment 88.5% of patients received greater than a 30% reduction in their VAS Pain Score. At 24 hours post treatment, as many as 80% of patients were still experiencing greater than a 30% reduction in their VAS pain score.

Reduction in VAS Pain Scores of at least 50% is considered even more significant for any type of pain treatment modality.

As shown in Table 5, When patients received a Biowave treatment, at 4 hours post treatment, as many as 85.0% of patients received greater than a 50% reduction in their VAS Pain Score. At 24 hours post treatment, as many as 70% of patients were still experiencing greater than a 50% reduction in their VAS pain score.

The results show that Biowave provides significant chronic pain relief for as many as 80% of patients treated at 24 hours post treatment.

Table 4

Percentage of Patients with >30% Reduction in VAS Pain Scores		
Time (Hrs)	**Deep pain**	**Surface Pain**
0	76.9%	80.8%
0.5	80.8%	80.8%
1	88.5%	88.5%
4	85.7%	95.0%
6	80.0%	90.0%
12	80.0%	85.0%
24	75.0%	80.0%

Table 5

Percentage of Patients with >50% Reduction in VAS Pain Scores		
Time (Hrs)	**Deep pain**	**Surface Pain**
0	69.2%	73.1%
0.5	65.4%	73.1%
1	69.2%	73.1%
4	81.0%	85.0%
6	75.0%	75.0%
12	70.0%	75.0%
24	65.0%	70.0%

5. Conclusions

The clinical results show that the Biowave System is safe, provides significantly better and longer lasting pain relief than TENS, and that the Biowave System provides pain relief for up to 24 hours for patients suffering from chronic low back pain.

6. Discussion Regarding Flawed Study Design

6.1 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.

6.2 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.

6.3 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 and longer lasting results as compared to TENS than those captured in this study.

6.4 Discussion Conclusions

Improvements to the study protocol design as described above would have resulted in the Biowave System having an even larger improvement and longer duration of pain relief versus TENS.