2001 Study on the Effectiveness of the Erchonia Low Level Laser in Providing Temporary Relief of Chronic Minor Neck or Shoulder Pain

**Erchonia Medical study submitted to the FDA and given market clearance January 2002.*

Abstract:

Background: This landmark study together with a companion 2000 study on pain reduction helped the Erchonia low level laser become the first low level laser of any kind to be approved by the FDA as safe and effective for treatment of chronic, minor pain.

Objectives: The purpose of this randomized, double-blind clinical study was to determine the effectiveness of the use of the Erchonia low level laser in providing temporary relief of chronic minor neck and shoulder pain. The primary outcome measure was the change in a subject's self-reported degree of pain using the Visual Analog Scale (VAS) from immediately prior to the treatment administered to immediately after the treatment.

Methods: 100 subjects were enrolled at three different test sites. A total of 86 subjects completed the study, 43 in each of the test and the placebo group. Subjects were randomly assigned to either the test or placebo group. Subjects in the test group received the actual laser procedure using the specified treatment protocol and subjects in the placebo group received a "fake" laser treatment.

Results: 28 (65.1%) of the test subjects met individual success criteria in improvement of pain, while only 5 (11.6%) of the placebo subjects met this criteria. The overall study success criteria, defined as at least a 30% difference between groups, was exceeded. The actual difference in the proportion of individual subject successes between test and placebo group subjects was 53.5%. Analysis of the primary outcome from the study using a one-tailed z-test found that the proportion of individual successes for subjects in the test group who had received the actual laser treatment was significantly greater than the proportion of individual successes for subjects in the placebo group who received the "fake" treatment.

Conclusion: The Erchonia low level laser is a safe and effective device for single-use temporary pain relief and improvement in range of motion for patients with chronic pain in the neck and shoulder areas originating from the conditions of osteoarthritis, muscle spasms and cervical and thoracic spine strain.

Key Words: Low level laser, low power laser, LLLT, chronic pain, osteoarthritis, muscle spasms, cervical and thoracic spine strain

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OBJECTIVES

The purpose of this multicenter clinical study was to determine the effectiveness of the use of the Erchonia PL2000 low level laser, manufactured by Erchonia Medical, the sponsoring company, in providing temporary relief of minor neck and/or shoulder pain of chronic origin by emitting 5 mw of near-infrared light (630 nm-640nm) to the affected area(s) for short durations.

As safety had been previously demonstrated, this study concentrated on effectiveness. The Erchonia laser is similar in its use and effect to other FDA Class II Medical Devices that are indicated for emitting infrared light at much higher energy levels in order to produce heat. The Erchonia laser is technologically different than these other devices, however, because it uses a much lower level of power and a slightly different light wavelength than the other Class II lasers. Therefore, the results of this study were used to

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support a request from the FDA for a *de novo* decision to place the Erchonia PL2000 into a Class I or Class II Exempt category based on the results of effectiveness. This landmark study together with a companion study in 2000 helped the Erchonia low level laser become the first low level laser of any kind to be approved by the FDA as safe and effective for single-use treatment of chronic, minor pain relief originating from conditions of osteoarthritis, muscle spasms, and cervical and thoracic spine sprain strain.

The Erchonia PL2000 is a safe device falling into a category of Class II laser under 21 CFR Part 1040, which makes it a chronic viewing hazard requiring long-term exposure in order to cause damage to the eyesight. Since the Erchonia PL2000 is in compliance with FDA's Performance Standards for Light-Emitting Products, the device is sufficiently labeled to protect the user and operator from harm. As an added precaution, the patients and doctors are supplied with protective eyewear that filters out red light.

ANTICIPATED RESULTS

Immediately following treatment administration with the laser, it was anticipated that the subjects in the test group would show a 30% reduction in self-reported overall degree of pain for the neck and shoulder regions and report some degree of satisfaction with the improvement in overall degree of pain attained.

For subjects in the placebo group, it was expected that there would likely be some placebo effect and would report some reduction in overall degree of pain and some degree of satisfaction but to a much lesser degree than the test group. The International Association for the Study of Pain reported that studies have consistently found that approximately 35% of placebo subjects in any type of study involving a placebo component respond to a placebo with some degree of pain relief.

Pain was measured by asking subjects to rate the level of pain on a Visual Analog Scale (VAS) from 1 to 100, both before and after the procedure. A universal inclinometer was used to measure range of motion, before and after each procedure.

METHODS

100 subjects were enrolled in this clinical study: 50 subjects in the test group and 50 subjects in the control group. Testing was done at three US clinical locations, with an approximately equal number of subjects (approximately 30 to 35 subjects) participating in the study at each location.

The sample size of 50 subjects per group was modeled after the Joseph Fleiss tables for determining reliable sample size for comparing two proportions and is based on: overall study success criteria of at least a 30% difference between groups, comparing the proportion of individual successes in each group. Individual subject success criteria was defined as a 30% reduction in degree of pain on the VAS immediately post-procedure compared to the initial pre-procedure degree of pain.

The Joseph Fleiss tables for determining sample size for comparing two proportions is 37 subjects per group. The final sample size in this study was 50 subjects per group in order to have sufficient numbers to ensure any significant differences between groups found could be considered statistically valid and representative of the general population being sampled.

Subjects were recruited from the investigators' normal pool of patients who come to their offices for treatment of pain. Patients only became subjects in this clinical study after they reviewed and discussed the informed consent form with the investigators and voluntarily signed the informed consent form. Subjects were not given money or any other form of compensation to participate in the clinical study, and they were not charged for the treatment.

To qualify for this study, patients had to satisfy each of the following inclusive-conditions criteria. Location of Pain: Patients must have presented with any one or more of chronic neck pain on the right side of the neck or the left side of the neck or the back of the neck; or chronic shoulder pain on the right shoulder and/or the left shoulder. Origin of Pain: A patient must have been diagnosed with any one or more of the following conditions including osteoarthritis, degenerative joint disorders or a degenerative joint disease. Chronic muscle spasms: involuntary contractions of a muscle or a group of muscles that was attended by pain and interference with function. Cervical and thoracic spine sprain produced by a

sudden stressful injury to the region causing stretching or tearing of the muscle/tendons/ligaments that resulted in pain and restricted range of motion. Medication Use History: history of taking muscle relaxants or anti-inflammatory medications, either over-the-counter and/or prescription medications. Stage of Injury: chronic, for osteoarthritis, chronic muscle spasms, and cervical and thoracic spine strain, a history of inflammation, spasm, or pain for more than 30 days.

To be eligible for participation in this clinical study, patients must have presented with a pre-procedure self-reported degree of pain of 50 or greater on the VAS pain scale that ranges from 0 (no pain) to 100 (worst pain imaginable).

Criteria for excluding patients from the study included patients presenting with an acute-stage pain condition, defined for each condition noted above but which had persisted for *less* than 30 days. Also excluded were patients with known herniated disc injuries or pain from conditions other than those specified in the inclusionary criteria above including the presence of infection or wounds, or pain from other bodily locations other than the neck and shoulder region. Patients were excluded who were under 18 or over 65 years of age, or were pregnant, or lactating. Patients were also excluded who had taken steroid, narcotic, OTC pain medications within 24 hours of the treatment.

Once a subject had been determined eligible for participation in the clinical study by the investigator and the subject agreed to participate by voluntarily signing the informed consent form, the doctor's office contacted the monitor of this study who acted as the central source for determining subject group assignment. This ensured that no investigator or other form of bias could occur in determining a subject's group assignment.

The monitor determined group assignment by drawing a number from a box that was specific to that clinical test site. Each test site box contained as equal as possible a number of folded pieces of paper that contained a '1' and a '2.' If the number '1' were selected, the monitor informed the investigator that the subject would be in the test group. If the number '2' were selected, the monitor informed the investigator that the subject would be in the placebo group.

Because the laser light on the laser device had to be turned off during the placebo trials, it was not possible for the investigator who administered the "treatment" to be blind to which group the subject belonged. In order to achieve as close to a double-blind study design as possible, a team of two qualified investigators working with each subject was created. One investigator (the "treatment" investigator) determined the diagnosis and eligibility of the subject for study participation and administered the "treatment" to that subject. This investigator was the only one to know to which group the subject was assigned and was the only investigator present in the room at any time during the treatment phase and did not participate in any way in any of the pre- and post-treatment evaluation activities performed by the "assessment" investigator.

The "assessment" investigator did not know to which group the subject was assigned since he was not present during the treatment phase – he was blind to the subjects' treatment group allocations and was not able to affect any bias on the pre- and post-treatment measurements.

The subjects were not told to which group they had been assigned. They wore special darkened protective glasses designed to filter out the laser light throughout the entirety of the treatment procedure so that they were not able to see if the light was on or off. As the laser light does not put out any notable degree of heat, this was not a distinguishing factor for subjects between the two groups.

The "assessment" investigator returned following completion of the laser treatment to request the subject's current self-reported degree of pain on the VAS. This measurement was taken within 3 minutes of the laser treatment.

Satisfaction Rating: subjects were asked to indicate how satisfied they were with the overall change in immediate pain level attained after the laser treatment using the following five-point scale: Very Satisfied, Somewhat Satisfied, Neither Satisfied nor Dissatisfied, Not Very Satisfied, Not at All Satisfied.

Both the subject and the "assessment" investigator were asked to indicate whether they believed the subject to have participated in the test group or the placebo group.

The "assessment" investigator determined the patient's post-treatment mobility in the neck-shoulder region using the universal inclinometer.

The study design was a single-treatment design to result in a labeling only for single-use pain relief. The design did not attempt to determine a length of time for which the laser would be effective. Any and all adverse reactions or events that occurred to any participating subject were recorded on the case report forms, and the investigator reported to the monitor as well as the Institutional Review Board any and all adverse reactions that did occur to any participating subject as a result of this clinical study.

RESULTS

Out of 100 subjects who began the trial, 14 were excluded for having taken pain or steroid medications, others were later found to have herniated disks, or fell under other criteria that the design of the study intended to exclude. 86 subjects qualified to complete the trials, 43 in the test group and 43 in the placebo group.

Of the final 86 subjects in the clinical study, 55 (64%) were diagnosed with multiple origins of pain, and 31 (36%) were diagnosed with a single origin of pain. Of the 82 (95.3%) subjects for whom medication use history was assessed, 48 (58.5%) reported a history of medication use that was relevant in formulating a final diagnosis, and 34 (41.5%) did not report a relevant medication use history.

A series of two-tailed t-tests of proportions to assess for differences in the average pre-procedure ROM values between test group and placebo group subjects, between test group and all subjects combined, and between placebo group and all subjects combined found no statistically significant differences at the $p<0.05$ significance level. A series of two-tailed t-tests of proportions was conducted to assess for differences in average pre-procedure ROM values between all group pairing combinations within and between clinical test sites. There were no statistically significant differences found for any of the group pairings at the $p<0.05$ significance level.

For all subjects combined, the decrease in average VAS rating attained from pre- to immediate post-treatment procedure was statistically significant at the $p<0.05$ significance level ($z=2.26$). For test group subjects, the decrease in average VAS rating pre- to immediate post-treatment procedure was statistically significant at the $p<0.05$ significance level ($z=2.82$). For placebo group subjects, the decrease in average VAS rating attained from pre- to immediate post-treatment procedure was not statistically significant at the $p<0.005$ significance level.

Subjects' degree of pain on the VAS were evaluated by the level of duration of pain they had experienced in the treatment area. Duration of pain was divided into four categories:

One month to 12 months (1 month –1 year): 22 subjects
13 months to 36 months (13 months-3 years): 20 subjects
37 months to 96 months (37 months – 8 years): 21 subjects
more than 96 months (more than 8 years): 23 subjects

Using a one-tailed z-test of proportions, a statistically significant improvement in degree of pain from pre- to immediately post-treatment was found for test subjects with a duration of pain between one and 12 months ($z=2.02$) at the $p<0.05$ significance level. Please note that this statistical testing was based on small sample sizes.

Using a series of one-tailed z-test of proportions, statistically significant improvements in degree of pain pre- to immediately post-treatment were found at the $p<0.05$ significance level:

Right Neck: Test Subjects: $z=1.96$
Right Shoulder: Test Subjects: $z=2.19$
Left Shoulder: Test Subjects: $z=2.15$

Test vs. placebo subjects

28 (65.1%) of the test subjects met individual success criteria in improvement of pain, while only 5 (11.6%) of the placebo subjects met this criteria. The overall study success criteria, defined as at least a 30% difference between groups, was exceeded. The actual difference in the proportion of individual subject successes between test and placebo group subjects was 53.5%. A series of one-tailed z-tests of proportions found that the percentage of test group subjects who met the individual subject success

criteria was significantly greater than the percentage of placebo group subjects who met the individual subject success criteria at each of the three clinical test sites.

Subject satisfaction ratings

Immediately following post-treatment pain ratings, subjects were asked to rate how satisfied they were with any changes in pain level they may have experienced compared pre-treatment feelings.

89.5% of subjects in the test group who had received the actual laser treatment were 'Satisfied' ('Somewhat' or 'Very') with the improvement in pain level attained compared with 34.3% of subjects in the placebo group who had not received the actual laser treatment. Using two-tailed t-tests of proportions, this difference was found to be statistically significant at the $p<0.0001$ significance level ($z=6.02$).

Perceived group assignment

After completion of the treatment administration, both the subject and the "assessment" investigator, who was blinded to the subject's group assignment, were asked to indicate to which group – test or placebo – they perceived the subject had been assigned.

78% of subjects in the test group accurately predicted their group assignment subsequent to treatment administration and 65.9% of subjects in the placebo group accurately predicted their group assignment. 85% of "assessment" investigators accurately predicted the group assignment of subjects in the test group subsequent to treatment administration and accurately predicted placebo group subjects' group assignment in 82.1% of cases. The implications of these perceptions were not analyzed.

Pre-Treatment vs. immediate post-treatment range of motion comparison

Statistically significant differences were found for the right shoulder, test vs. placebo subjects: 15.35 degrees improvement in ROM for the test group compared with 3.48 degrees improvement in ROM for the placebo, respectively ($z=2.26$, $p<0.05$). For the left shoulder, test vs. placebo subjects: 13.37 degrees improvement in ROM for the test subjects compared with 1.70 degrees improvement in ROM for the placebo group, respectively ($z=2.10$, $p<0.05$).

Adverse events and reactions

No subject reported any relevant adverse event or reaction after completion of the treatment.

BACKGROUND: MECHANISMS OF PAIN REDUCTION & RELATED CLINICAL STUDIES

Guyton (1991), a renowned expert on the physiology of pain, explains that there are two leading causes of pain: 1) Muscle Spasm and 2) Tissue Ischemia.

Muscle spasm is a common cause of pain and is the basis of many clinical pain syndromes. This pain results partially from the direct effect of muscle spasm in stimulating mechanosensitive pain receptors. It possibly also results from the indirect effect of muscle spasm to compress the blood vessels and cause ischemia. A spasm increases the rate of metabolism in the muscle tissue, at the same time making the relative ischemia even greater, creating ideal conditions for release of biochemical pain-inducing substances.

Tissue Ischemia: When blood flow to a tissue is blocked, the tissue becomes painful within a few minutes. The greater the rate of metabolism of the tissue, the more rapidly the pain appears. If a blood pressure cuff is placed around the upper arm and inflated until the arterial blood flow ceases, exercise of the forearm muscles can cause severe muscle spasm within 15 to 20 seconds. In the absence of muscle exercise, the pain will not appear for 3 to 4 minutes.

One of the suggested causes of pain in ischemia is accumulation of large amounts of lactic acid in the tissues, formed because of the anaerobic metabolism that occurs during ischemia. It is also possible that other chemical agents such as bradykinin, proteolytic enzymes, and other chemical mediators, are formed in the tissues because of cell damage and that these, rather than lactic acid, stimulate the pain nerve endings.

Low level laser as a pain reduction modality

When ischemia or muscle spasm is reduced, pain will be reduced. When transmission is inhibited by tactile sensory signals, the degree of pain experienced is also reduced. All of these modalities can be and are accomplished using low level laser energy. By applying laser energy in low levels to affected areas, the frequency of sensory nerve firing is increased, which subsequently increases the frequency of stimuli to the spinal cord, brain stem and brain, in turn inhibiting pain at the spinal cord and brain stem levels.

Given that the instigation of pain and the resulting degree of pain experienced are governed by physiological and biophysical rules, it can be deduced that the reduction or elimination of pain is also governed by an equally solid set of rules. Guyton explains the rules of pain elimination/reduction as follows: Several clinical procedures have been developed recently for suppressing pain by electrical stimulation of large sensory nerve fibers. The stimulating electrodes are placed on selected areas of the skin, or implanted over the spinal cord to stimulate the dorsal sensory columns.

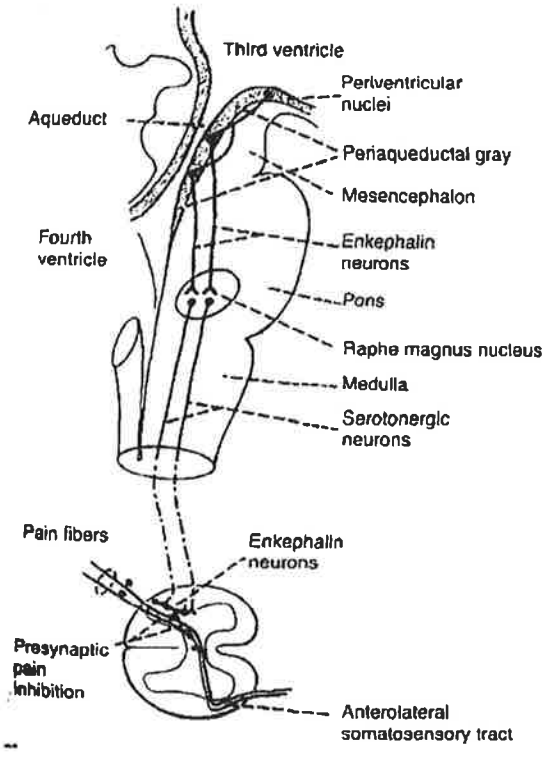
Another important landmark in the saga of pain control was the discovery that stimulation of large sensory fibers from the peripheral tactile receptors depresses the transmission of signals either from the same area of the body or even from areas sometimes located many segments away. This effect presumably results from a type of local lateral inhibition. It explains why such simple maneuvers as rubbing the site of pain are often very effective in relieving pain. It probably also explains why liniments are often useful in the relief of pain. This mechanism and simultaneous psychogenic excitation of the central analgesia system are probably also the basis of pain relief by acupuncture.

When peripheral nerves are lasered, they send sensory information into the spinal cord, up the brain stem to the brain. Guyton explains that there are three major analgesic centers or areas for pain control: one is located in the spinal cord and the other two are located in the brain stem.

The degree to which each person reacts to pain varies tremendously. This results partly from the capability of the brain itself to control the degree of input of pain signals to the nervous system by activation of a pain control system, called an analgesia system.

Analgesia system

The analgesia system consists of three major components (plus other accessory components): (1) the periaqueductal gray area of mesencephalon and upper pons surrounding the aqueduct of Sylvius; neurons from this area send their signals to (2) the raphe magnus nucleus, a thin midline nucleus located in the lower pons and upper medulla. From there, the signals are transmitted down the dorsolateral columns in the spinal cord to (3) a pain inhibitory complex located in the dorsal horns of the spinal cord. At this point, the analgesia signals can block the pain before it is relayed to the brain.



In addition to increasing stimuli to the spinal cord, brain stem and brain, low level laser energy reduces inflammation caused by ischemia and excess amounts of lactic acid and other muscle irritants. Elimination of muscle spasm and ischemia reduce pain.

The hypothesis that low level laser treatment (LLLT) can be effective in pain reduction has also been demonstrated by Bjordal (2003) for reducing pain in chronic joint disorders, Gur et al (2003) in reducing chronic back pain, and Kulekcioglu et al (2003) in reducing pain in temporomandibular disorders, among others. Anders et al (1993), Snyder et al (2002) and Medrado (2003) have also demonstrated that LLLT promoted nerve regeneration, enhanced healing, and reduced inflammation.

Coupled with the anti-inflammatory and immune enhancement properties of low level laser energy, inflammation is decreased and normal nerve function can be restored.

CONCLUSION

The Erchonia low level laser is a safe and effective device for single-use temporary pain relief and improvement in range of motion for patients with chronic pain in the neck and shoulder areas originating from chronic conditions of osteoarthritis, muscle spasms, and cervical and thoracic spine sprain strain. This landmark study together with a companion 2000 study on pain reduction helped the Erchonia low level laser to become the first low level laser of any kind to be approved by the FDA as safe and effective for treatment of chronic, minor pain.

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