ORIGINAL ARTICLE

Pain Patients Prefer *Artemisia californica* Liniment to Placebo in a Community-Based Trial

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ABSTRACT

Background: Pain is not adequately treated with currently available medicines.

Methods: Pain patients were recruited in a community setting and treated with placebo followed by a liniment made from sagebrush (*Artemisia californica*). Each patient assessed their pain before treatment, after placebo treatment, and after liniment treatment.

Results: The majority received some pain relief from the placebo. Most patients, 98%, preferred the liniment to the placebo.

Conclusions: This community-based trial provides evidence to support the performance of a clinical trial of *A. californica* liniment in pain patients.

Key words: *Artemisia californica*, sagebrush, liniment, pain, chronic pain, community-based study

INTRODUCTION

The authors intended to perform a clinical trial of *Artemisia californica* liniment. However, insufficient data are available to support an application for a clinical trial. Therefore, a community-based trial was performed. No randomized, placebo-controlled clinical trials have been performed with this liniment.

The liniment made from *A. californica* has been used by the authors to treat many pain patients over the years.[1,2] The recipe for making the liniment has been published and is used by many people to make their own liniment.[1,3,4] Patients with broken bones, gunshot wounds, car accident trauma, bicycle accident trauma, gout, arthritis, neuropathy, bee stings, migraine headaches, and many other conditions have been effectively treated with the liniment. Pain relief is very rapid, usually starting within about 20 s and increasing afterward for several minutes.[1,3,4]

The liniment contains at least 15 monoterpenoids[1,5] that inhibit transient receptor potential cation (TRP) channels in the skin. All of these monoterpenoids have been identified in the previous studies that employed gas chromatography/mass spectrometry (MS) and high-performance liquid chromatography/MS.[1,5] Skin TRP channels are the major pain receptors in the body and are densely present in the skin.[6] Monoterpenoids quickly penetrate into the skin, inhibit TRP channels, relieve pain, and evaporate from the skin. Pain relief with monoterpenoids does not require penetration into the blood. This makes pain relief with the liniment rapid and very safe.

Placebos are useful in the treatment of pain. A meta-analysis of pain studies found that orally administered placebos decrease pain by about 6.5%.[7] The body makes endocannabinoids, enkephalins, endorphins, and other pain relieving compounds. Placebos may be able to stimulate the production of these compounds.[8,9]

METHODS

The liniment was made from *A. californica* collected in the private garden of JA. The leaves and branches (86 g) were transferred into amber-colored glass jars. One leaf of *Salvia apiana* and one seed of *Persea americana* cut in quarters were added. The jar was filled with about 500 mL of 70% isopropanol. This was placed in a dark area for 6 weeks to form the liniment. The liniment was put into 177 mL amber plastic bottles and applied by spray to painful areas of the skin. Each application of the liniment supplied 1 mL of liniment onto the skin. All patients received between 1 and 5 sprays (1–5 mL) of liniment depending on the site of pain. Most pain was treated with three sprays. However, lower back pain and knee pain were treated with 3–5

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sprays because of the amount of skin area that needed treatment. For knee pain, the entire knee area, front and back, was sprayed.

The placebo liniment consisted of 70% isopropanol. It was used in the same kind of bottle with a spray top as the liniment. Patients were not told and could not tell which bottle contained liniment or placebo. The investigators knew which bottle contained placebo and which bottle contained the liniment.

Patient Selection

Patients (*n* = 74) volunteered to participate in this community-based trial while attending talks about plant medicines presented by the authors. Each patient was given the opportunity to read and sign a consent form in accord with the Helsinki Declaration. Each patient could decline or withdraw from the study at any time. Patients were not diagnosed for the cause of their pain, but reported their doctors' diagnoses. The number of women recruited was 61 and 13 men [Table 1]. All patients claimed to be adults with 32 above retirement age. Patient characteristics (*n* = 74) were as follows: Senior is 65 years old and above (*n* = 32), middle aged is 30–65 years old (*n* = 40), and young is below 30 years old (*n* = 2). No children, under the age of 21, were treated. Most patients declined to state their race. The authors did not attempt to identify their race.

An investigational new drug application was submitted to the US Food and Drug Administration (FDA) to perform a clinical trial with the liniment. The FDA denied the application stating that safety of the liniment must be proved in two animal species. Funding to perform a study in two animal species could not be found. No application was filed with the Institutional Review Board to perform a clinical trial because the board requires FDA approval. Instead, the authors performed a community-based trial that does not require institutional approval. The FDA guidance on waiver of Institutional Review Board review states that "You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations." The authors are protected by California State Law SB577 that allows "access by California residents to complementary and alternative health care practitioners who are not providing services that require medical training and credentials."

Procedure

Each patient was asked to report the level of their pain on a scale of 0–10. They were sprayed with the placebo on a painful area of their skin. After 20 s, they were asked to evaluate their pain. They were then sprayed on the same spot of skin with *A. californica* liniment. Twenty seconds later, they were asked to evaluate their pain.

RESULTS

All but a few patients (98%) reported *A. californica* liniment was superior to placebo [Table 2]. *A. californica* liniment provided significant pain relief. The placebo used was an active placebo, since evaporation of isopropanol from the skin cools the skin and inhibits temperature-sensitive TRP channels,[6] thereby decreasing pain. The placebo decreased pain in 43 out of 64 patients, 67%. Pain relief ranged from 0 to 7 out of 10. A few patients (*n* = 10) were treated only with placebo and reported that pain relief lasted from 15 to more than 60 min. These patients were then offered *A. californica* liniment.

Table 1: Pain sites (*n*=77), characteristics, and approximate amount of liniment applied.

Painful site	Number of patients	Level of pain	Amount of liniment used (mL)	Pain relief (average)
Knee	13	1–10	5	4
Groin	4	2–5	3	3.3
Shoulder	10	2–8	4	3.8
Elbow	3	2–3	3	2.3
Hand	11	2–7	4	3.5
Ankle	2	4–6	4	4
Foot	2	5–7	4	5
Neck	13	4–9	3	4.6
Lower back	9	2–7	3–5	3.4
Hip	2	2–5	3	3
Cancer area	1	7	5	4
Peripheral neuropathy	2	3–6	3	6
Headache	2	1–7	1–2	3.5
Fibromyalgia	2	9	3	9
Abdomen	1	5	3	5

Table 2: Pain data comparisons

Before treatment mean, SD	Placebo treatment mean, SD	Liniment treatment mean, SD
$p<0.05$		$p<0.05$
5.1	3.2	1.1
2.0	2.4	1.4

Each patient reported their pain on a scale of 0–10 before treatment, after placebo, and after liniment. Comparisons used ANOVA and Tukey's test. Before treatment was significantly different from liniment treatment (n=64)

A. californica liniment decreased pain beyond placebo in 57 patients, 89%. In seven patients, *A. californica* liniment did not improve pain relief more than the placebo. These were patients whose pain decreased to 0 or 1 after placebo treatment. However, all but one patient (n = 63) said that they preferred *A. californica* liniment rather than the placebo. No patient suffered the return of pain during the study period, which was 1 h. None of the patients experienced toxicity or adverse effects from the placebo or *A. californica* liniment.

Patients had a wide range of painful areas including leg, knee, shoulder, ankle, head, back, groin, hand, finger, foot, toe, and abdomen. A few patients had pain in both hands or wrists allowing separate treatment of both sides. Painful conditions reported were ankylosing spondylitis, cancer metastasis into bone, fibromyalgia, neuropathy, shingles, systemic lupus erythematosus, migraine headache, chronic back pain, and whiplash.

DISCUSSION

The use of *A. californica* liniment to treat pain is rapid and effective. Previous reports found that pain relief with the liniment lasts for 6–8 h in patients with arthritis, neuropathy, gout, and other conditions.[1,2] Several patients have been using the liniment daily for 10 years or more without adverse events, addiction, or tolerance. *A. californica* liniment is also anti-inflammatory since it inhibits neurogenic inflammation.[10] A few patients were able to prevent hip or knee replacements using the liniment daily for months or years.

Chronic pain patients find the liniment useful since it inhibits the pain chemokine cycle in the skin that is important in chronic pain.[2,11] Skin sensory neurons secrete chemokines that attract monocytes and neutrophils into the skin.[2,10,11] Monocytes become skin macrophages, produce prostaglandins and more chemokines that activate skin-resident T cells and transactivate TRP channels on sensory neurons to increase pain.[10] These T cells produce interleukin-17 that induces more chemokine release in the skin.[10] Chemokines activate ascending neural pathways to the brain stem and brain that activate chemokine production in other sites of the body.[10] Neutrophils secrete leukotrienes that cause long-lasting pain.[10] Prostaglandins cause pain and induce the phosphorylation of TRP channels that make long-lasting pain.[10] The skin produces pain in chronic pain.

Monoterpenoids and sesquiterpenes in the liniment inhibit chronic pain in the skin. Several patients have reported the liniment cured their chronic pain, such as whiplash, after using it daily for about 5 weeks.[2] Cure means that the pain is permanently gone and does not return. Opioid addiction has been successfully treated in several patients with the liniment. This involves daily use of the liniment for pain while decreasing opioid dosage by half weekly. Opioids can make pain worse (opioid-induced hyperalgesia) by inducing chemokine production throughout the body, especially fentanyl.[12,13]

Placebo treatment provided substantial pain relief in many patients. The patients who did not get pain relief from the placebo were in the most pain and reported that their initial pain was between a score of 7 and 10. The study period, 1 h, was not long enough to find the duration of placebo pain relief in some patients. However, other patients said their pain returned in 15–30 min after placebo treatment.

Several patients, especially those in pain above a score of 5, were highly skeptical that the liniment would provide pain relief for them. They all expressed that they were convinced the only way to treat pain was with oral or injected analgesic agents. A few of these patients had to wait several minutes before they could conclude their pain had been diminished by the liniment.

The skin is the organ that senses pain.[14-16] The brain and brainstem process pain sensations from the skin. Deep organs, including bones, all have neural projections to the skin allowing for pain perception.[14,15] A myocardial infarction is usually felt in the skin of the left arm or shoulder due to neural projections into the skin of these areas. Some internal pain is very difficult to treat, such as kidney stones, because the source of the pain may move creating new pain.

CONCLUSIONS

The current study provides evidence that pain is effectively and rapidly treated in the skin with a liniment containing a mixture of several monoterpenoids and sesquiterpenoids. The liniment is also very safe since it evaporates from the skin without having to penetrate into the blood. This approach should be investigated in a clinical trial.

AUTHORS' CONTRIBUTIONS

All authors treated patients and recorded pain records. *A. californica* liniment and placebo were made by J.D.A. All authors contributed to writing the manuscript. All

authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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