REVIEW ARTICLE

Preliminary Observations of a Novel Topical Oil with Analgesic Properties for Treatment of Acute and Chronic Pain Syndromes

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■ **Abstract**

Objective: Essential oxygen oil (OxyRub™ from CreoMed Inc., Naples, FL, U.S.A.) is a novel topical analgesic currently commercially available in Europe and now available in the U.S.A. It represents an important alternative to other treatments (nonsteroidal anti-inflammatory drugs, acetaminophen, menthol, camphor) for managing mild to moderate acute and chronic pain. Several clinical trials of this oil will be reviewed.

Results: One large ($n = 455$) open-label trial found essential oxygen oil to be a safe and effective analgesic for a broad range of patients with acute and chronic pain. In that study, 80% of patients reported that their pain decreased by more than 75%. A double-blind placebo-controlled study ($n = 50$) found significant pain reduction for tendonitis in patients using essential oxygen oil. Another trial of essential oxygen oil vs. placebo ($n = 50$) with various pain diagnoses found that 98% of patients with various pain diagnoses reported "very good" pain relief in the oil group compared to 48% in the placebo group. Furthermore, a randomized controlled trial in 10 women to measure oxygen microcirculatory effect in the skin showed an increased microcirculatory effect with improved oxygenation (increased partial pressure of oxygen in the skin) after application of essential oxygen oil. In all studies, the oil was well tolerated. None of these studies has been previously published.

Conclusions: Based on studies completed, essential oxygen oil has shown itself to be safe, has demonstrated positive analgesic effects for the treatment of acute and chronic pain, and has improved oxygen content in the skin as well as other dermatological parameters. ■

Key Words: analgesia, non-narcotic analgesics, nonopioid analgesics, topical administration, low back pain, arthritis, complementary medicine, alternative medicine

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INTRODUCTION

An estimated 50 million Americans live with chronic pain brought on by disease, disorder, or accident with an additional 25 million Americans suffering acute pain.[1] A survey by the Centers for Disease Control and Prevention found 10% of American adults report having pain that lasted a year or more; at age 65 years, this increased to 60%.[2] The financial impact of pain is difficult to quantify. In the year 2000, 36 million Americans missed work in the previous year because of pain and 83 million Americans stated that pain had limited their activities.[1] The National Institutes of Health assesses that pain costs the U.S. economy in excess of $100 billion annually in health-care expenditures and lost productivity.[3] Pain contributes to over 50 million lost workdays per year in the U.SA.[4] While we may attempt to quantify the cost of pain to the nation in terms of lost productivity and health-care expenditures, it is impossible to measure the true scope of damage inflicted by chronic pain on the lives of individuals and their families.

Pain is complex because it has both physical and mental components and must be assessed subjectively. It is now believed that gender, ethnicity, emotion, and other factors play a role in pain perception, pain threshold levels, and responsiveness to treatment.[5,6] Furthermore, patients metabolize pain medications differently. It has been widely observed that analgesics have side effects in certain patients but not others, and the degree of severity of those side effects may differ as well. Medication that is effective in 1 patient may be less effective in the next and not effective at all in another.

In this regard, topical preparations represent a useful alternative to systemic medications. Pharmacological activity is localized to the area of application, which may limit systemic exposure and thus reduce the potential for any systemic adverse events (AEs) or drug interactions.[7–10] Topical remedies may be more acceptable to patients who, for a variety of reasons, refuse or resist systemic medication.[8] Topical analgesics are included in the current Osteoarthritis Research Society International recommendations for the management of osteoarthritis of the hip and knee.[11] In the case of nonsteroidal anti-inflammatory drugs (NSAIDs), a meta-analysis of data revealed that the effectiveness of treatment with topical NSAIDs was equivalent to that of orally administered NSAIDs.[12]

Health-care professionals need access to a range of therapeutic options to manage chronic pain patients. In the U.S.A., there are many different over-the-counter (OTC) analgesics in oral and topical formulations. However, recent reports on NSAIDs suggest that tolerability in the form of serious AEs, marginal efficacy, or both may limit patients' ability to achieve adequate pain relief with these drugs.[13–15]

Essential oxygen oil, also known as peroxide oil (OxyRub, CreoMed, Naples, FL, U.S.A.), is a novel topical medication made from naturally occurring ingredients and possessing analgesic as well as anti-inflammatory properties. Its base compound has been marketed for nearly 4 decades in the European Union with well documented experiences in more than 1 million pain patient exposures. It is available OTC and has been the subject of several clinical studies.

BACKGROUND

Pain is the most common symptom for which people seek medical attention.[16] Acute pain affects between 15% and 20% of the U.S. population annually, and between 25% and 30% of the U.S. population experiences chronic pain.[17] However, despite the high prevalence of pain, it is often underdiagnosed and undertreated. In a recent multispecialty survey, only about half (51%) of physicians believe that they manage patients' pain well ("good" or "very good").[18]

Arthritic pain and inflammation of the joint complex (bursitis, tendonitis, sprains, strains, and acute pain) and repetitive stress injuries (including but not limited to carpal tunnel syndrome) are common complaints, often treated with NSAIDs or acetaminophen, available in many formulations both OTC and by prescription. In the U.S.A., 46.5 million noninstitutionalized adults have been diagnosed with arthritis (roughly 20% of the population) and there were over 11 million ambulatory care visits with a primary diagnosis of osteoarthritis and allied disorders in 2006 alone.[19] These conditions are often treated with acetaminophen or NSAIDs.

Acetaminophen products should not be taken in excess or used with alcohol.[20] NSAIDs are not appropriate from the outset for certain patients, and their long-term use for the treatment of chronic pain in any patient is not without risk. NSAIDs are associated with many apparently dose-dependent side effects,[21] including gastrointestinal AEs,[22] renal toxicity,[23] cardiovascular events,[24] including possibly myocardial infarction,[25] and hypertension.[26] For those reasons, there are large groups of patients, eg, heart failure patients, for whom NSAIDs are inappropriate.[24]

Drug-related AEs with NSAIDs range from mild to severe, even life-threatening. Recently updated Ameri-

can Geriatric Society guidelines for pain management in the elderly state that long-term NSAID therapy should be considered only when other pain relievers have failed, including opioids. This document states, "For many patients, chronic opioid therapy, low-dose corticosteroid therapy (for those with inflammatory conditions), or other adjunctive drug strategies (eg, the use of antidepressants or anticonvulsants for neuropathic pain) may have fewer life-threatening risks than does long-term daily use of high-dose NSAIDs."[27]

Furthermore, the Food and Drug Administration (FDA) will soon require NSAIDs and acetaminophen to carry labeling warning consumers about potential safety risks, including internal bleeding and liver damage, when such drugs are taken in excess or along with certain other drugs, such as anticoagulants or steroids. While some manufacturers of these products have voluntary included warnings in their labeling as early as 2006, the 2009 regulations go beyond these preliminary warning statements. All such products must be in compliance with this regulation by April 30, 2010.[28] The impact of these warnings remains to be seen, but it is likely to cause some consumers to seek alternative OTC pain remedies.

While opioid therapy may be proposed as an alternative to NSAIDs and acetaminophen for patients suffering from moderate to severe chronic pain, the use of opioids remains controversial. Opioids are both effective analgesics and controlled substances; the risk of abuse, addiction, and diversion limits their use to selected patients. The manufacturers of 24 specific opioid extended-release pain medications have been notified by a letter from the FDA that they will be required to submit a risk evaluation and mitigation strategy report.[29] While the outcome of this new governmental scrutiny remains to be seen, it is likely that many physicians will refuse to prescribe opioids, even when they are indicated and an appropriate therapeutic choice for a given patient.

For these reasons, alternative approaches to pain relief are urgently needed for patients with such common pain disorders as arthritis, strains, sprains, acute injuries, and other chronic pain conditions. In fact, specialty societies such as the Arthritis Foundation[30] and prestigious medical organizations, including the Mayo Clinic,[31] suggest complementary or alternative therapies for the treatment of some arthritic conditions to avoid the adverse effects of certain medications. The use of complementary or alternative medicine (CAM) has increased substantially since 1990, and this growth is attributable to an increased percentage of the population seeking alternative therapy rather than increased visits per individual patient. In 1997, 42.1% of adult Americans sought some form of alternative therapy during the year in 629 million visits (vs. 386 million visits to a primary care provider); CAM was most frequently sought for chronic conditions such as back problems, headaches, and depression.[32] In 2007, roughly 40% of American adults had used CAM in the past 12 months.[33]

HISTORY

In the 1950s, Professor Pierre Baranger of the Pasteur Institute in France traveled to India to research chaulmoogra oil, an important therapeutic agent in certain medical traditions but virtually unknown in the West. There, he discovered that the "secret" to the oil's medicinal properties was a traditional method of preparation which required the oil to be aged in open, shallow vessels exposed to sun and air for periods of many years. The slow oxygenation process along with simultaneous exposures to ultraviolet radiation created a hyperoxygenated oil with anti-inflammatory properties.

Back in Europe, Baranger was able to vastly accelerate the peroxidation process to a matter of days in the laboratory, using other oils. The hyperoxygenated, peroxidized, triglyerol-oxyester-rich oil that he created in the lab is the basis for the current formulation of the novel pain oil described in this article: 93% photo-oxygenated peanut oil or corn oil, 7% oil of rosemary combined to create a clear oil of low viscosity. Recently, subsequent formulations include various concentrations of camphor.

MODE OF ACTION/REACTION

Essential oxygen can be applied directly to the site of pain, where it demonstrates pain relief, healing, and anti-inflammatory properties. The mechanism of action of essential oxygen oil is not known,[34] but is likely multifactoral involving accelerated blood flow deep in the superficial vascular network. Its anti-inflammatory properties are thought to include modulation of superoxide dismutase (SOD), an enzyme in the pain cascade that catalyzes the destruction of superoxide, a free radical that occurs naturally in the body with a scavenging function to kill invading microorganisms. When superoxide reacts with SOD, its main reaction is within itself (dismutation) or another biological radical such as nitric oxide. Since superoxide is one of the main reactive oxygen species in the cell, SOD is one of the body's main antioxidants. SOD is also used in cosmetic products to

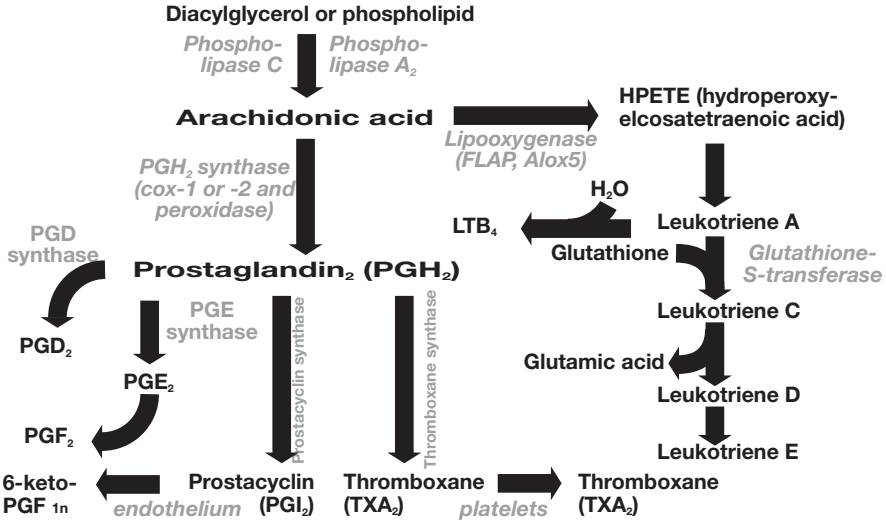

Figure 1. In the arachidonic cascade, arachidonic acid is freed from the phospholipid molecule by phospholipase A. Essential oxygen oil affects the arachidonic cascade and blocks the action of phospholipase A, which would have caused further inflammation.

reduce free radical damage and there is evidence that SOD can reverse fibrosis.[35] Essential oxygen oil is thought to be a SOD mimetic. Furthermore, superoxide is thought to be a factor in glutamate-induced pain. Overproduction of glutamate, the most abundant excitatory neurotransmitter in humans, is believed to play a role in pain from inflammatory processes and in cancer and neuropathic pain.

An overproduction of superoxide creates oxidative stress, which has been associated with a wide range of conditions including systemic inflammatory response syndrome,[36] sepsis,[37] acute respiratory distress syndrome,[38] ischemia-reperfusion,[39] trauma, and burns.[40] The morbidity and mortality associated with critical illness can be positively correlated with the patient's degree of oxidative stress.[41]

A surrogate marker for oxidative stress is the plasma levels of malondialdehyde (MDA).[42,43] As a SOD mimetic, the oil reduces oxidative stress and lowers MDA, which is thought to be a pain mediator. MDA can be found in tissue sections from the joints of patients suffering from osteoarthritis.[44] The literature currently reports associations between high levels of plasma MDA and vascular pain,[45] acute coronary syndromes,[46] pain from pancreatitis,[47] peripheral neuropathy,[48] temporomandibular joint disease,[49] fibromyalgia,[50] acute abdominal pain,[51] and primary dysmenorrhea.[52] This list is not exhaustive and indicates the growing body of evidence associating elevated serum MDA levels with pain.

In addition to its antioxidant effect, essential oxygen oil also has an anti-inflammatory effect. Both prostaglandins and leukotrienes are known to mediate inflammation and are produced in the arachidonic cascade. Arachidonic acid is an omega-6 polyunsaturated fatty acid found in skeletal muscle membrane phospholipids; arachidonic acid is freed from the phospholipid molecule by phospholipase A in the arachidonic cascade. Essential oxygen oil is an optimal enzyme inhibitor that specifically inhibits PLA2 activity on neural cell membranes already inflamed and under oxidative stress. This, in turn, halts the action of phospholipase A (Figure 1).

By comparison, the mechanism of action of diclofenac, similar to that of NSAIDs, is known to inhibit the enzyme cyclooxygenase, an early component in the arachidonic cascade, resulting in the reduced formation of prostaglandins, thromboxanes, and prostacyclin. It is unclear how reduced synthesis of these components results in therapeutic efficacy.

STUDIES

A variety of clinical studies have already been conducted using this pain oil formulation created by Dr Baranger, although these studies have not been published in the literature. There are reports in which the oil was found effective in relieving diaper rash, pruritus, and increasing blood flow.[53] More comprehensive studies are described in detail below.

OPEN-LABEL TOLERABILITY STUDY

Method

Under the direction of Dr Jean-Yves Arramon in France, an open-label study was conducted ($n = 445$) on patients with acute or chronic traumatic, inflammatory, or degenerative painful muscle conditions.[54] Patients

presented to one of several health-care professionals or clinics: a rheumatologist, a gerontologist, a specialist in physical medicine with a physiotherapist, and/or a general practice (ambulatory clinic). The study included patients of both genders and all ages with no exclusion criteria other than known skin allergies. Patients were given the topical oil to apply manually to the afflicted area from 1 to 4 times daily (mean = 2). Physicians could alternatively prescribe that oil-soaked compresses be applied to the painful area and changed every 24 hours. In principle, the duration of treatment was a minimum of 8 days, and the treatment duration varied depending on symptoms. Patients were asked to refrain from the use of any other analgesics during their treatment with the pain oil, other than as prescribed by the physician previously.

Patients were then asked to evaluate how effective the oil was based on the clinical criteria of: pain, heat, swelling, stiffness, and mobility. Patients could rate these categories from 0 (completely absent) to +++ (very severe). The investigators also examined the patients to assess for signs of clinical tolerance as well as any AEs. Investigators were advised to screen for any signs of local irritation or cutaneous allergy, in particular.

Results

At baseline, the patient population was 61% male with a mean age of 45.2 years and a variety of diagnoses (Table 1). A total of 42.5% of patients had chronic pain.

Many patients were treated for fewer than 15 days (48%), but nearly as many (42%) were treated from 16 days to 6 months. About 10% were treated for more than 6 months. Upon enrollment into the study, nearly all patients had pain and related symptoms (Table 2).

During the study, almost half of the patients (48.3%) had no adjunctive therapy. A subset of the patients (about 35%) received rehabilitative or physical therapy and slightly over 16% took analgesics, including, but not limited to, NSAIDs.

At the conclusion of treatment, global results found that 77.5% rated their experience with the pain oil as "excellent" or "good"; 15.1% rated it as "moderate"; and 7.4% rated the outcome as "no improvement" or that their condition worsened. In 211 subjects (47.5%), the onset of action from first application of the oil to relief was within the first 48 hours. Based on clinical findings, nearly 80% of patients reported that pain was improved by at least 75% (Table 3).

Furthermore, experiences were relatively similar in the acute and chronic subsets (Table 4).

Oil tolerability was assessed by interviewing and examining the patients. Clinical tolerance was excellent in the majority of cases (96.2%) and treatment was suspended in <1% of cases. No allergic reactions were observed. In the cases of "moderate" tolerance, redness, heat, and slight but transient pain were found (Table 5).

Table 1. Patients at Baseline in Arramon Study of Acute snd Chronic Pain Syndromes

Indications	Number of Patients (Percentage)
Arthroses (knee, thumb, etc.)	111 (25)
Post-traumatic pain, postoperative pain, sequelae of fractures	103 (23)
Tendonitis	80 (18)
Back pain (cervical or thoracic pain, lumbago)	78 (17)
Muscle spasms	44 (10)
Sprains	23 (5)
Interphalangeal arthritis	3 (1)
Related conditions (post-herpetic neuralgia, sunburn)	3 (1)

Table 2. Clinical Signs and Symptoms of Patients upon Enrollment in Arramon Study

Clinical Sign	Number of Cases (Percentage)
Pain	309 (99.7)
Impaired mobility	254 (82)
Stiffness	251 (81)
Swelling	97 (31)
Heat	90 (29)

Table 3. Reduction in Signs and Symptoms from Baseline to Conclusion of Treatment in Arramon Study

Clinical Symptoms and Signs	Percentage at Baseline	Percentage Reporting Improvement of ≥75%
Pain	99.7%	79.8%
Impaired mobility	82%	66.8%
Stiffness	81%	67.4%

Table 4. Comparison of Results in Pain Self-Assessment between Acute and Chronic Pain Patients in Arramon Study

Patient Subset	Excellent or Good	Moderate	No Improvement or Condition Worsened
Acute or subacute (57.5%)	83%	9%	8%
Chronic conditions (42.5%)	70%	21%	9%

Table 5. Tolerability of Treatment in Arramon Study

Clinical Tolerance Rating	Number of Cases (Percentage)
Excellent	428 (96.2)
Good	11 (2.5)
Moderate	5 (1)
Poor with discontinuation of treatment	1 (0.3)

Discussion

This was an open-label study of a wide range of patients with both acute and chronic pain of different etiologies. The vast majority of patients reported "excellent" or "good" analgesic response with "good" to "excellent" clinical tolerability. This suggests to the authors that the essential oxygen oil is a suitable analgesic for a broad range of acute and chronic pain applications. Best scores were achieved for pain relief, an area of particular concern for many patients.

Because of the excellent tolerability of this product, the authors feel that it can be recommended for general topical use for many types of painful conditions. In particular, this product may be useful for patients who for a variety of reasons cannot take or do not respond well to conventional oral analgesics. Furthermore, it may be used by those who wish to minimize their use of drug therapy while still achieving reliable pain relief. The essential oxygen oil may work well as an adjunctive therapy when pain is not well controlled by other combination treatment options.

This study had several limitations. It was open-label, which may allow for some investigator bias. There was no placebo control for comparisons. Pain studies rely on subjective reporting, and there is at least the potential for underreporting or overreporting.

Study Conclusion

This novel pain oil is very well tolerated and provides good pain relief to patients with pain, stiffness, and impaired mobility. Its excellent tolerability and good broad analgesic effect make it appropriate for use in a wide range of patients. Further studies are warranted to increase the scope of use.

ACUTE TENDONITIS STUDY

Method

Under the direction of Dr Renée-Liliane Dreiser in France, a double-blind placebo-controlled trial was conducted on patients between the ages of 18 and 70 years of age ($n = 50$) presenting with acute tendonitis of the upper or lower limbs, including "tennis elbow," painful shoulders, heels, and thumbs.[55] Exclusion criteria included chronic tendonitis (>1 month), calcification of the shoulder, ruptured rotator membrane, and tendonitis that required or would require orthopedic intervention. Patients were randomized into 2 arms, one of which received the essential oxygen oil and the other a placebo (similar container but containing only ordinary oil and fragrance). Patients were asked to apply about 2 mL of the oil manually to the affected area twice daily and massage it into the skin. A compress with the oil was then applied and held in place with a bandage. Bandages, compresses, oil, and other supplies were provided by the clinic. At the conclusion of the treatment, oil content in the bottles was measured to assess compliance. Compliance was considered good if the patient had oil left over consistent with no more than 1 day's missed treatment; average if 3 days' worth of oil remained; and bad if there was 4 or more days' worth of oil left over.

Figure 2. Huskisson scale for self-assessed pain relief.

Physicians were free to prescribe rest to patients, but no physical therapy, adjunctive treatments (ice, mud, etc.), corticoids, analgesics by injection, or NSAIDs were allowed; however, certain analgesics (paracetamol, glafenine) were permitted under supervision. Patients who had taken NSAIDs before entering the study had to observe a period of 48 to 72 hours of therapeutic withdrawal (washout period) before they could enter the study.

Patients evaluated their pain relief based on the Huskisson visual scale, assessing pain along a 100-mm line ranging from no pain (one end) to unbearable pain (other end) (Fig. 2). They were asked to evaluate both spontaneous pain and pain that occurred during movement. Pain was further assessed verbally using a 4-point subjective categorical scale (no pain, mild pain, average pain, severe pain). Subjects were also asked to evaluate whether pressure or opposed mobility caused pain, whether there was active or passive articular mobility, and if they woke at night from pain. Furthermore, physicians evaluated the patient in terms of how effective the treatment was and the time it took to obtain analgesic response as well as side effects. Patients were treated for a period of 7 days.

Results

Two patients were lost to follow-up and all other patients' compliance was rated as "good," meaning they missed no more than 1 day's worth of medication. Of the 48 patients who participated in the study, 25 were in the control group. Thirty of the patients were female and the average age was 40.9 years. Patients had a variety of diagnoses (Table 6) with 21 involving an upper and 17 involving a lower limb. Most patients presented with conditions of traumatic or post-traumatic etiology (Table 7). There were not statistically significant differences between the groups except in terms of gender, in that there were more women in the control group (but because of the relatively small size of the patient population, comparisons were still made in the study).

The main evaluation method was the Huskisson scale with results tabulated into numerical values. Patients evaluated their pain at baseline (prior to treatment) and on the seventh day post-treatment. Results showed a significant reduction in pain after treatment ($P < 0.001$) for both study groups (Table 8).

Pain was also assessed verbally during rest, movement, and pressure, using a scale of 4 grades (0 was no pain, 3 was severe pain). The test was conducted before and after treatment. Data were analyzed once using the Mann and Whitney test, which notes statistically significant differences post-therapy if groups were similar at the outset (Table 9). Although the small patient population made meaningful statistical analysis impossible, before treatment, 6 patients from the treatment group and 7 patients from the control group reported waking several times in the night due to tendonitis. Post-treatment, those numbers were 2 patients from the treatment group and 4 patients from the control group who reported waking several times in the night due to tendonitis.

At the conclusion of treatment, patients and physicians were asked to evaluate the global effectiveness of the remedy on a scale of 1 (improved), 2 (the same), or 3 (worse) (Table 10).

Thirty-one of the patients (18 from the treatment and 13 from the control group) reported the number of days it took to see an improvement. The mean scores for the treatment group were 4.8 ± 1.8 days vs. the control group 5.8 ± 1.5 days. Taking patients who reported no improvement and the total patient population into

Table 6. Pain Diagnosis or Location for Patients at Baseline in Dreiser Study

Diagnosis	Treatment Group	Control Group
Upper Limbs		
Radials	1	1
Supraspinal	3	1
Long biceps	2	2
Epitochlea	2	1
Epicondyle	3	3
Thumb	3	5
Shoulder	1	3
Subtotal upper limbs	15	16
Lower Limbs		
Equinus deformity of the foot[61]	2	3
Trochanter	1	3
Tibilais anterior	1	0
Rotular tendon	0	1
Achilles tendon	4	2
Subtotal lower limb	8	9

Table 7. Etiology of Pain in Dreiser Study ($n = 50$)

	Traumatic and Post-traumatic	Sports	Occupational	Other	Not Specified
Treatment group	9	5	0	5	4
Control group	11	3	0	5	6

Table 8. Pain Scores based on Huskisson Pain Scale (Visual Analog Scale) in Dreiser Study at Outset and Post-Treatment in Dreiser Study

	Average score at outset	Average Score after Treatment	Change
Treatment group	63.39 + 10.04 mm	27.43 + 16.5 mm	↓ 58%
Control group	68.44 + 10.35 mm	39.48 + 19.9 mm	↓ 42%

Table 9. Pain Scores Based on a Four-Point Verbal Assessment Scale in Dreiser Test when Injured Area was at Rest, Moving, or Pressure Applied. In this Verbal Scale, 0 was no Pain and 3 was the most Severe Pain

	Rest		Movement		Pressure	
	Improved	Worsened	Improved	Worsened	Improved	Worsened
Treatment group	11	0	19	4	21	2
Control group	9	6	15	8	17	6

Table 10. At Conclusion of Dreiser Study, both Physicians and Patients were asked to Rate the Global Effectiveness of the Pain Oil on a Scale of 1 (Improved), 2 (The Same) or 3 (No Change)

	Doctor		Patient		
	Improved (1)	No Change (2)	Improved (1)	No Change (2)	*P* Value
Treatment group	18	5	20	3	$P < 0.06$
Control group	20	3	13	12	$P < 0.01$

Table 11. Physician Evaluation of Effectiveness And Tolerance of the pain Oil in the Dreiser Study on a Four-Point Scale (Excellent, Good, Fair, Zero)

	Excellent	Good	Average	Zero
Treatment group	5	8	5	5
Control group	0	6	8	11

Table 12. Rigal Study Patients at Baseline by Diagnosis and by Treatment Group versus Control Group

	Number of Patients	
Diagnosis	Essential Oxygen Oil	Placebo
Muscular and peri-articular pain	8	12
Traumatic, postfracture or postoperative pain	11	8
Arthritic pain	3	4
Inflammatory pain	2	1
Sciatic neuralgia	1	0

account, the estimated time to improvement was 7 days (Student's *t*-test, t = 2.071 or $P < 0.05$).

No patients had to discontinue use of the treatment because of poor tolerance. In the treatment group, there were 2 cases of erythema and pruritus reported. Both local reactions occurred on day 4 and resolved within a week.

Physicians were asked to evaluate the treatment overall based on their observations of effectiveness and tolerance. When results were compared ("excellent" and "good" compared to "average" and "zero"), the treatment achieved significantly better results compared to the control group ($P < 0.05$) (Table 11).

Discussion

This study was a small, double-blind, placebo-controlled trial of the essential oxygen oil treatment vs. a placebo in 48 patients being treated for tendonitis. Statistically significant results favoring the essential oxygen oil treatment were obtained in several areas:

- Evaluation of pain on Huskisson's scale ($P < 0.025$)
- Spontaneous pain evaluation at rest ($P < 0.05$)
- Time to improvement ($P < 0.05$)
- Patient's opinion of treatment ($P < 0.02$)
- Doctor's final assessment ($P < 0.05$), in addition to which, the number of "good" results is significantly higher in the treatment group vs. placebo group

Results trended toward significance in favor of the treatment group in the category of assessment of pain during movement ($P < 0.06$). Tolerance was comparable in both groups with only 2 cases of localized reactions (erythema, pruritus) which resolved within a week.

Study Conclusion

Although the patient population in this study was small and there were gender imbalances in control and treatment arms at baseline, rigorous methodology was used. A marked placebo effect was observed, which is not unusual in topical analgesia studies.[56–58] While the pain oil provided good pain relief with few side effects, further studies are suggested to test its analgesic properties on a broader spectrum of patients.

RIGAL STUDY

Method

Fifty adult patients were randomly divided into 2 groups to compare essential oxygen oil to placebo in patients with various pain diagnoses[59] (Table 12). Patients with skin allergies were excluded. Signs and symptoms were scored from 0 (absent) to ++++ (extremely severe) pre- and post-treatment. Investigators evaluated clinical tolerance on a 4-grade scale from 0 (no results) to +++ (excellent results).

In the patient population, 44% had pain for 1 month or less, while 10% had pain for over 1 year upon enrollment into the study.

Results

Of the patients in the essential oxygen oil group, 98% evaluated their results as "excellent" or "good." In the placebo group, 48% found their results "excellent" or "good." Using Yates correction, the difference achieved statistical significance in favor of essential oxygen oil. In the essential oxygen oil cases, 72% of patients reported results within 10 days or less. The oil was effective against all of the clinical symptoms evaluated (pain, heat, swelling, mobility, and stiffness). Tolerance was excellent in all subjects; no localized reactions were observed.

Discussion

The authors found the results of this study quite promising, in that it found that patients with a wide variety of pain diagnoses were able to achieve relatively rapid, effective pain relief with no adverse reactions. The range of pain diagnoses makes it impossible to draw statistically significant conclusion by pain category.

Conclusion

This study was encouraging that essential oxygen oil is a safe, effective topical pain reliever for a wide variety of painful conditions.

SKIN MOISTURE CONTENT AND PROFILOMETRY STUDY

Several studies were conducted at the Ludwig-Maximillian-University's Institute of Medical Balneology and Climatology with regard to dermatological properties of essential oxygen oil. The studies examined skin moisture content and profilometry, partial pressure of oxygen measurement, dermatological examination, and visual analog scale (VAS) evaluation before, during, and after administration of various trial drugs. The randomized, controlled trial ($n = 10$, all female) measured oxygen microcirculatory effect in the skin and demonstrated increased microcirculatory effect with oxygen microcirculatory effect on the skin. Oxygenation improved, as shown by increased partial pressure of oxygen in the skin, after application of essential oxygen oil.

Method

A randomized, double-blind clinical trial ($n = 10$) was conducted on females (mean age 34) to evaluate a number of dermatological parameters after twice-daily applications of essential oil (vs. control) for 4 weeks. Subjects had to be nonsmokers with no skin disorders or known allergies.

Oil was applied on 3 separate locations, no less than 5 cm each, on the inside of each patient's forearm between the elbow and wrist. Randomization occurred in that neither subjects nor investigators knew which of the numbered applications contained the active ingredients.

The following measurements were taken in a climate-controlled room:

- Microcirculation using Laser Doppler Flow movement, using the Periflux instrument (Perimed KB, Sweden).
- Skin temperature
- Corneometer skin moisture content
- Transdermal measurements of the partial pressure of oxygen (pO2) using the 361 SM Oxymonitor (Hellige, Freiburg, Germany)
- Noninvasive profilometry using the 970 Quantimet Analysis apparatus (Cambridge Instruments, Bensheim, Germany) for the structural analysis of the epidermis
- VAS assessment of the patient's subjective skin assessment
- Dermatological exam in which a dermatologist evaluated the patient's skin condition

Results

There was a measurable but nonsignificant increase in oxygen in the skin with essential oxygen oil vs. placebo. Microcirculation improved (Fig. 3). There was a clear

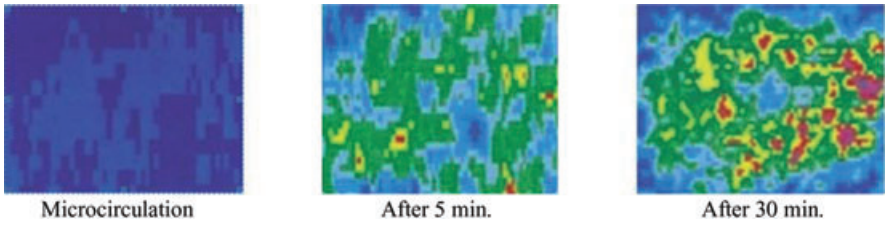

Figure 3. Microcirculatory results taken before application of essential oil (far right), 5 minutes post-application, and then 30 minutes post-application. Yellow and red areas indicate increased microcirculation.

and measurable increase in skin moisture content during the treatment with the active ingredient; this increase varied with the length of treatment. The main effect occurred in the initial 2 weeks, but moisture continued to increase over the 4-week period. The difference did not achieve statistical significance.

The epidermal structure was evaluated with noninvasive profilometry and found that skin smoothness improved and skinfold count decreased with treatment compared to placebo. While the difference was measurable and observable, it was not statistically significant. When allowing a 2% error factor, a skinfold count decreased in association with length of treatment.

The VAS assessment allowed subjects to evaluate their skin on a scale from 0 to 10 (0 is worst and 10 is "excellent"). No differences were observed. No AEs were reported.

Discussion

These several tests on a small patient population found measurable results in terms of dermatological skin properties, but results failed to achieve statistical significance. The small and limited patient population (only women aged 26 to 50 years with no allergies, skin disorders, hematological disorders, and who were not pregnant, smokers, or alcohol abusers) made it difficult for results to achieve statistical significance, although there were observable differences favoring the essential oxygen oil in all but the visual assessment.

Study Conclusions

The findings from this study suggest that moisture content, skin quality, partial oxygen pressure, and other dermatological parameters were not worsened and possibly improved with treatment. While this study drew no significant conclusions, it strongly emphasizes the need for greater investigation into these dermatological properties with regard to this essential oxygen oil.

POST-MARKET SURVEILLANCE

Method

One hundred American patients with various acute pain symptoms used essential oxygen pain oil and were mailed a questionnaire, which could be returned anonymously. The study had a 10% response rate ($n = 10$) and NEMA Research, Inc. conducted the evaluation.[60]

Results

At baseline, 30% had been using the essential oxygen oil for more than 6 months and the average use was 1 to 6 months. The majority (60%) learned about the oil "from a friend," and the majority (80%) used the product more than once a week (50% used the product daily). All respondents were either "very satisfied" or "satisfied" with the essential oxygen oil. Seventy percent of respondents were "very satisfied" with the product and no respondent was "dissatisfied." Ninety percent said the product quality was "high" and "much better" than comparable products on the market. Every respondent in the survey reported that he or she intended to continue using the product (100%).

Table 13. Post-Market Surveillance Results Obtained by Questionnaire Stating Specific Improvements

Improvements
75% reported an improvement in joint flexibility
80% reported fewer sleep disturbances due to pain
100% reported improved ability to work because of reduced pain
100% reported higher energy levels due to reduced pain
100% found this product reduced pain better than other medication(s) they had used
70% said their pain was reduced by 70% or more

Pain relief was evaluated by questionnaire: 40% reported 100% pain relief; 50% reported greater than 90% pain relief; and 70% reported greater than 70% pain relief. Specific improvements appear in Table 13.

Discussion

Patients found the pain oil to be effective, of high quality, and better than other market alternatives. Intriguing is the fact that the majority of respondents tried the product based on "word of mouth," indicating that users of the product were pleased enough to recommend it to others. Furthermore, it suggests that pain patients are actively looking for alternative pain relief treatment.

Questionnaires are thought to sometimes skew responses, but the questions and anonymity were intended to help allow for genuine feedback, whether negative or positive. In particular, patients surveyed in this study reported practical improvements in daily living as a result of this treatment: better sleep, higher energy levels, and better ability to work.

Conclusions

Patients reported good results with this pain oil product and recommend it to their friends; the majority use the product regularly (80% once a week, 50% daily) and

considered the product to be better than comparable alternatives. No patients discontinued the treatment for any reason and 100% intended to continue using it; the survey supports the premise that the product is well accepted by patients.

CONCLUSIONS

Essential oxygen oil is a topical analgesic new to the U.S.A., but its base compound has been used with good results in Europe for more than 15 years. Its introduction to America is timely, in that Americans increasingly are receptive to alternative treatments for chronic pain and both prescription and OTC pain relievers are coming under increased governmental scrutiny. While the exact mechanisms of action of essential oxygen oil are not clearly understood, it appears, in clinical studies, to increase microcirculation and block the arachidonic cascade. Recent clinical studies described herein consistently show that essential oxygen oil is an effective topical analgesic, suitable for use in a broad range of acute and chronic diagnoses. In these studies, essential oxygen oil was safe, well tolerated, and generally well accepted by patients. Essential oxygen oil may appeal to health-conscious consumers in that it contains natural ingredients and no steroids. The studies evaluated in this article found essential oxygen oil was safe and effective for patients with arthritis pain, low back pain, acute tendonitis, sciatica, traumatic and postoperative pain, and inflammatory pain. A post-marketing surveillance study found 100% of patients reported essential oxygen oil reduced pain better than other medications they had used and 70% estimated that essential oxygen oil reduced their pain by 70% or more. While further testing of essential oxygen oil is warranted, particularly in view of its properties for specific types of pain or in specific subpopulations of patients, these several clinical studies confirm that this is a safe, effective, and well-tolerated topical analgesic.

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