Evaluation of a novel topical essential oxygen oil for the treatment of pain in acute tendinopathy and sprains

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Summary

Topical analgesics may play an increasingly important role in managing acute and chronic pain as acetaminophen, NSAIDs, and opioid drugs come under heightened scrutiny. This article reviews studies about essential oxygen oil, a topical over-the-counter (OTC) analgesic new to the American market but available for many years in Europe. Prospective studies evaluating the oil's safety and efficacy in acute and chronic pain patients, a dermatological study in which healthy subjects served as their own controls, and a post-marketing surveillance study were considered. These studies found the novel essential oxygen oil to be safe and effective in a variety of acute and chronic pain syndromes as well as being well tolerated with few side effects. Its mechanism of action is not understood and further study is warranted. Essential oxygen oil is safe and effective for the treatment of pain associated with many common conditions, including tendinopathy, arthritis, sprains, and others.

Key Words: analgesia, topical analgesic, essential oxygen oil, acute pain, chronic pain, tendinopathy.

Introduction

Pain is an epidemic, with 10% of American respondents in a survey by the Centers for Disease Control and Prevention reporting chronic pain of at least one year's duration (1). This is more than the number of people in America living with diabetes (2) and HIV (3) combined. Yet despite its ubiquity, pain is not well managed.
Conventional medicine approaches pain primarily with systemic agents, but evidence is large and growing that systemic analgesics can be dangerous (4,5). Opioids are effective pain-killers but bring with them the potential for tolerance, addiction, withdrawal, and diversion. Prescription opioid abuse has become alarming enough to prompt government intervention; the FDA is mandating risk-evaluation and mitigation strategy (REMS) reports from many opioid manufacturers (6). Even apparently benign over-the-counter (OTC) remedies such as acetaminophen and NSAIDs have recently come under increased scrutiny with new, stronger warning labels required by the government by April 2010 (7). The American Geriatric Society has updated its guidelines on pain to recommend that older Americans seeking relief from moderate to severe chronic pain be given opioid analgesics rather than acetaminophen or NSAIDs (8). Topical analgesics appear to offer the benefit of localized action, but reports of their effectiveness are mixed: the effectiveness of topical capsaicin for neuropathic pain was modest (9); topical rubefacients (salicylate-based products) are not effective for acute and chronic pain (10); while topical NSAIDs are effective in osteoarthritis of the knee (11). Many different types of topical analgesics exist and reports which do not clearly differentiate the products by types (some of which are more effective than others) have led to some confusion about these topical pain relievers (12).
As doubt and restrictions are cast on some of the mainstays of the analgesic armamentarium, clinicians are still confronted with the urgent and unmet need to help patients safely and effectively manage acute and chronic pain. The current economic and national healthcare crises have exacerbated the situation to the point that many patients no longer have the financial means to seek pain relief in conventional medicine. Among other patients, particularly those who have been misdiagnosed or inadequately treated, there is a real crisis of confidence that medicine can offer safe and effect treatments for pain. Respected medical or-

ganizations, such as the Mayo Clinic, (13) and specialty societies, such as the Arthritis Foundation (14) and the American Headache Society, (15) recommend complementary and alternative therapies for treating pain. About 40% of Americans have used a complementary or alternative medical (CAM) therapy in the past year, (16) frequently for analgesia (17).

Topical analgesics seem particularly apt to help meet this unmet need, despite their relative paucity on the market. Topical analgesics aim to limit pharmacological activity to the application site, reducing the risks of systemic exposure (18) (19). The Osteoarthritis Research Society International (OARSI) recommends topical analgesics for the treatment of pain associated with osteoarthritis of the knee and hip (20). An analysis of data for topical versus systemic NSAIDs found both formulations to be equivalent in terms of effectiveness (21). A meta-analysis of topical NSAIDs found them safe and effective in the treatment of acute pain over the course of one week (22).

This article reviews essential oxygen oil. While essential oxygen oil is a new product to the American market, it has been available in Europe for more than a decade and traces back to a pain oil product from ancient times. Today's formulation of essential oxygen oil is based on the discovery of a healing oil in India by Dr. Pierre Baranger of France. Dr. Baranger, a devout Christian, speculated that the healing properties of the oil applied to the battered robbery victim in the Biblical parable of the Good Samaritan were based on medical fact (23). In India, he learned of an ancient healing oil which was made from chaulmoogra tree oil left to oxidize in shallow vessels over many years in natural light. Returning to France, Baranger accelerated the oxidation process and introduced to Europe a basic formulation of pain oil which is sold commercially in Europe as a pain comfort oil.

Methods

To date, there has been little in the literature about essential oxygen oil (24). However, five clinical trials have recently been concluded on essential oxygen oil, none of which have been published by investigators in peer-reviewed journals. Since these clinical trials were small in scope and dealt with a relatively obscure product, it is unlikely that, on their own, they will be published. For that reason, the authors sought to summarize and evaluate them here.

PubMed search for the term "OxyRub" produced one result (24). A search for "essential oxygen oil" produced only numerous references for unrelated topics and products. For this narrative review on OxyRub, the authors assessed data on file (CreoMed Inc., Naples, FL USA) on file and grouped together unpublished observations and smaller studies

The clinical studies discussed in this article included patients with a variety of painful diagnoses and were designed with differing endpoints. (Arramon JY. Clinical file: Matiga.; Dreiser RL. Clinical report on Matiga oil, double-blind trial; Rigal J. Double-blind trial in comparison with a placebo to evaluate the effectiveness and clinical tolerance of Matiga oil; Study of the administration of VIA NOVA 960-13. Post-market surveillance study. NEMA Research, Inc. All of them are Data on files - See Table 1).

Where a placebo was used, an ordinary oil in a similar-looking container was provided to patients. In all studies, tolerability of the essential oxygen oil was assessed. Essential oxygen oil has been marketed in a variety of formulations; it has been available in Europe for over a decade.

Results

Tolerability Study

In a double-blind, placebo-controlled tolerability study, 345 patients of 445 (77.5%) reported global effectiveness as "excellent" or "good," with 67 patients (15.1%) reporting "moderate" results, and 33 patients of 445 (7.4%) reporting no changes or worsening of their condition. More patients with acute pain syndromes reported "excellent" or "good" results (369 patients of 445; 83%) than patients with chronic pain conditions (70%), but patients who reported no changes or worsening of their condition were about the same (8% acute, 9% chronic). Patients were asked if the essential oxygen oil improved their condition by 75% or more in terms of pain (present in 444 patients of 445 at baseline (99.7%), stiffness (81% , 360 patients of 445), and altered mobility (82%, 365 patients of 445). The majority of patients reported 75% or greater improvement: 79.8% in terms of pain, 67.4% in terms of stiffness, and 66.8% in mobility. Clinical tolerance in this study was evaluated both by the patient and by a local clinical examination. The vast majority of patients (428 patients of 445, 96.2%) reported excellent clinical tolerance. No side effects or allergic reactions were reported.

Acute tendinopathy Study

In the tendinopathy study by Dr. Dreiser, statistically significant differences in favor of the essential oxygen oil over placebo. Among other points, patients were asked to evaluate their pain using a visual analog scale (VAS) known as the Huskisson pain scale (see Figure 1). Patients are asked to indicate where their pain levels are along a continuum; the Huskisson scale allows pain to then be "measured" in centimeters or inches.

Among the results of the acute tendinopathy study are the following:

- Pain evaluation using the Huskisson pain scale ($p<0.025$)
- Spontaneous pain evaluating at rest ($p<0.05$)
- Time taken for improvement ($p<0.05$)
- Patient's opinion/satisfaction with treatment ($p<0.01$)
- Doctor's final assessment ($p<0.05$)

Pain during movement was evaluated on a verbal scale with 0 classified as "no pain," 1 as "slight pain," 2 as "moderate pain" and 3 as "severe pain." Assessments were made pre-treatment and then post - treatment. Before treatment, 12 patients in both treatment and control groups rated their pain as moderate (2) and 11 patients in both treatment and control groups rated their pain as severe (3). Following treatment, the treatment group had two patients with no pain (0), 16 patients with slight pain (1), 3 patients with moderate pain (2), and two patients with severe pain (3) compared to the control group where no patients reported absence of pain (0), 14 reported slight pain (1), 5 patients reported moderate pain (2), and four reported severe pain (3). While patients in the treatment group overall reported less pain, the difference was not statistically significant ($p<0.06$).

Rigal Study

The Rigal study found significantly more patients (Yates

Table 1 - Clinical studies overview for essential oxygen oil.

	Tolerability Study [36]	Acute tendinopathy Study [37]	Rigal Study [38]	Dermatology Study [39]	Post-market Surveillance Study [40]
Study Design	Open-label	Double blind, placebo controlled	Double blind, randomized, placebo controlled	Blinded, randomized, placebo-controlled	Retrospective (questionnaire)
Patient Population	445	50	50	10	10
Mean or average age	Mean: 45.2 years	Average: 40.9 years	Mean: active 46.2, placebo 49.5 years	Average: 34 years	Not stated
Gender	61% male	40% male	42% male	100% female	Not stated
Pain Diagnoses	Inflammatory or degenerative muscle conditions	Acute tendinopathy of upper or lower limbs	Various: muscular pain, traumatic or post-op pain, arthritic pain, inflammation, sciatica	None	Various
Endpoints	Pain relief, stiffness, mobility	Pain relief, response time	Pain relief, heat swelling, mobility, stiffness	Dermatological parameters, including microcirculation, skin temperature, corneometer skin moisture content, transdermal measurements of partial pressure of oxygen	Pain relief, satisfaction
Acute or chronic	Both (57.5% acute)	Acute	Both (38% acute)	N/A	Chronic
Duration	Min. 8 days	7 days	2-8 days	28 days	Various
Study director	Dr. Jean-Yves Arramon	Dr. Renée-Liliane Dreiser	Dr. Jean Rigal	University of Munich	NEMA Research
Location	France	France	France	Germany	USA

Figure 1 - Huskisson pain scale, a visual analog scale for patient assessment of pain levels.

corrections x>0.001) rated essential oxygen oil in terms of global results as "excellent" or "good" compared to placebo. Markedly more patients rated the essential oxygen oil superior to placebo in study parameters, which were categorized as pain, heat swelling, and stiffness. These clinical signs were assessed by the investigator. See Table 2. No allergic reactions or side effects were observed.

Dermatology Study

The dermatology study did not evaluate analgesia; indeed, patients had no pain syndromes. Instead, patients compared dermatological parameters of the essential oxygen oil versus placebo by applying both oils to their arms. (Patients served as their own controls). This study resulted in measurable but non-significant increases in oxygen in the skin and improved microcirculation (see Figure 2). The main effect was noted in the first two weeks of application, but moisture in the skin increased over the entire four-week course of the study. This difference did not achieve statistical significance.

Table 2 - Percentage of patients in Rigal study who rated these parameters as "excellent" or "good" on a four-point scale (excellent, good, mediocre, nil).

	Essential Oil	Placebo
Pain relief	92%	40%
Heat	100%	50%
Swelling	100%	60%
Mobility	77%	6%
Stiffness	100%	30%

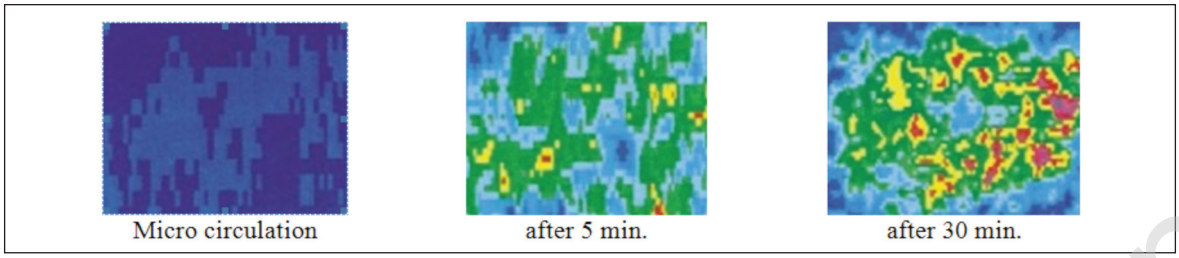

Figure 2 - Microcirculation was visibly improved within 30 minutes in patients using essential oxygen oil. These images were taken with a laser Doppler perfusion imager (633 nm, Moor® LDI, 630 HeNe), single application of about 5 mg/cc on the inside of the underarm. The colors indicate the degree of circulation: blue is pretreatment, green indicates an increase in circulation up to about 25%, yellow an increase of up to 50%, and red an increase of about 100% compared to the initial value. The image on the left was obtained before treatment; the center image was taken five minutes post-application of essential oxygen oil. The image on the right was obtained 30 minutes post-application of essential oxygen oil.

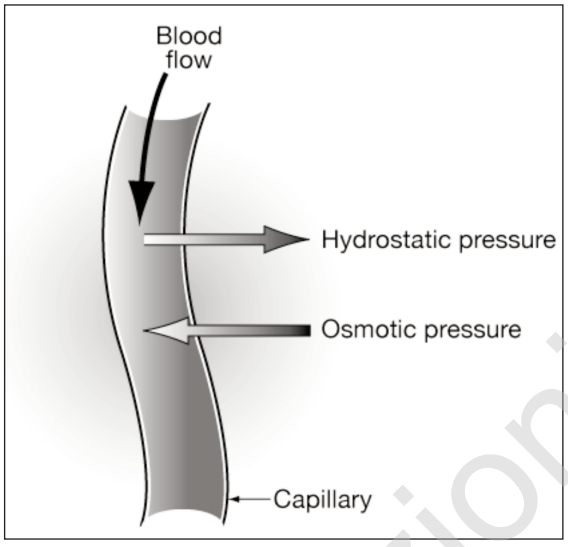

Figure 3 - The microcirculatory system relies on a balance of hydrostatic and osmotic pressure.

The microcirculatory system is a complex network of small vessels that transport blood to and from the organs to regulate tissue perfusion, blood pressure, fluid levels in tissue, body temperature, and to regulate the supply of oxygen and removal of carbon dioxide and other metabolic wastes. (25) Microcirculation has been previously studied and there is evidence in the literature that therapies which can affect the microcirculation may be associated with pain control (26,27). See Figure 3.

Post-Marketing Surveillance Study

The post-marketing surveillance study was a retrospective questionnaire sent out to 100 patients (response rate 10%, n=10) who had been using essential oxygen oil for one to six months. Half of these respondents (50%) used the essential oxygen oil daily and 100% were "very satisfied" or "satisfied" with the product. In terms of quality, 90% rated essential oxygen oil quality as "high" or "much better" than comparable products. Every respondent (100%) stated his or her intention to continue to use the product. In this study, 75% reported improved joint flexibility and 80% stated they had fewer sleep disturbances caused by pain than previously. All patients (100%) in the post-marketing surveillance study reported improved ability to work and higher energy levels attributable to better pain management. An overview of the results from four of these studies (excluding the dermatology study) appears in Table 3.

Mechanism of Action

The exact mechanism of action of essential oxygen oils is unknown, however different hypothesizes include a biomechanical process and a physiochemical process related to their various fatty acid components (chaulmoogric, hydnocarpic, gorlic acids; linoleic acid; oleic and palmitic acids; carnosic, hormelic and rosemarinic acids) (28). The later, may work to inhibit lipid peroxidation or limit the arachidonic acid pathway or both. Lipid peroxdiation occurs when reactive oxygen species (ROS), such as superoxides, overwhelm the body's natural defenses. ROS are free radicals (molecules with an odd number of electrons) or are molecules that initiate processes that create free radicals. Free radicals attack and damage cells creating oxidative stress. Free radicals are not readily observable in biological samples, so serum malondialdehyde (MDA) levels are widely used as a surrogate endproduct of lipid peroxidation and, thus, free radical damage to lipid molecules. MDA has also been associated with pain levels, (29) but it is thought that it is a marker of free radical damage rather than a causative factor for pain. By disrupting lipid peroxidation, components of essential oxygen oil may reduce free radical damage.

Certain fatty acids (linoleic, oleic, and plamitic acid) have been shown to have an anti-inflammatory effect in that they interrupt the anarchidonic cascade by inhibiting the formation of pro-inflammatory products from arachidonic acid metabolism and produce, instead, substances that have an anti-inflammatory effect (15-lipoxygenase products) (30-34). Essential oxygen oil functions like naturally occurring body enzymes, that is, superoxide dismutase (SOD) a free-radical scavenger and catalyst, an enzyme which converts hydrogen peroxide to water and oxygen. By combating the toxic action of reactive oxygen species (ROS) and hydrogen peroxide, essential oxygen oil helps protect the skin from free-radical damage and skin aging while supporting healthy cell metabolism.

While it is known that some of the components in essential oxygen oil formulations are capable of activating certain analgesic pathways, it remains unclear how and to what extent this is accomplished. It has been speculated that there are possible synergistic effects of the components in the oil. The clinical studies we reviewed assessed safe-

Table 1 - Clinical studies overview for essential oxygen oil.

	Tolerability Study [36]	Acute tendinopathy Study [37]	Rigal Study [38]	Post-market Surveillance Study [39]
Pain relief	77.5% "excellent" or "good"	Pain reduced by 58% with oil ($p<0.025$)	98% "excellent" or "good"	40% reported 100% pain relief; 70% reported >70% pain relief
Adjuvant analgesics	Yes (51.7%)	Yes but limited	No	Not controlled
Onset of action	<2 days (47.5%)	7 days	<10 days (72%)	n/a
Pain improved by at least 75%	79.8%	n/a	n/a	70% reported improvement of >70%
Excellent clinical tolerance	96.2%	21.7%	100%	n/a
Tolerance evaluated	Patient, clinician exam	Patient, clinician exam	Clinician exam	n/a
Allergic reactions	0	0	0	Not reported
Treatment halted	<1%	0	None	n/a
Side effects	None	Erythema, pruritus (2 cases)	None	None

ty and efficacy of the product and not the mechanism of action but the results of these studies indicate that a better understanding of the mechanisms of action is warranted.

Discussion

CAM treatments are increasingly accepted in medicine and with that acceptance comes an expectation to provide clinicians with evidence-based data in support of product use. However, large-scale, randomized, placebo-controlled clinical trials are often financially or logistically out of reach for CAM products despite the reasonable need for clinicians to evaluate evidence when making prescribing decisions and recommendations. In the case of essential oxygen oil, a novel product on the American market but an established OTC analgesic in Europe, some clinical evidence does exist to inform clinical practice.

In the United States, essential oxygen oil is available as an OTC topical analgesic (OxyRub™, CreoMed, Naples, FL) is made from corn or ground nut oil subjected to an accelerated peroxidation process to create a triglycerol-oxyester (TGO) oil. When applied to the site of pain, it has been observed to provide deep, penetrating, rapid-onset, long-lasting pain relief, healing, and anti-inflammatory properties. The exact mechanism of action of essential oxygen oil remains unclear (OxyRub™ prescribing information. CredoMed, Inc. Naples, FL), but may involve the microcirculatory system and hinibition of lipid peroxidation or limitations to the arachidonic acid pathway or both. Essential oxygen oil in similar formulations has been available in Europe for over 15 years and has been the subject of numerous but small clinical studies.

The studies presented here, to the best of the knowledge of the authors, represent the full scope of completed clinical trials involving essential oxygen oil. They are admittedly diverse, in that they evaluated different aspects of the product in different patient populations with different objectives. Nevertheless, taken together, they provide an overall picture of safety and potential efficacy on the use of essential oxygen oil for treating pain.

Overall, essential oxygen oil was found to be an effective analgesic for many types of acute and chronic pain syndromes, including such common conditions as tendonitis, arthritis, muscle sprains, and post-surgical pain. The oil is well tolerated with few side effects and no allergic reactions.

Although perhaps not medically persuasive, the evidence supporting patient acceptance and satisfaction with essential oxygen oil is clinically important. In the post-marketing surveillance study, more than half of the patients (60%) tried essential oxygen oil based on the recommendation of a friend, indicating that patients using essential oxygen oil liked it well enough to suggest it to others. The authors believe that there are reasons beyond safety and efficacy to support this high level of patient approval, including a desire to use a topical rather than systemic analgesic, preference for natural ingredients, ease of application and use, and a desire to find an alternative to NSAIDs and other analgesics, particularly for chronic conditions. Moreover, a high level of patient acceptance may translate into improved adherence to treatment directions.

While there are several clinical studies supporting essential oxygen oil than support some other CAM products in use today, there is still a need for further evaluation. A better understanding of its mechanism of action is desired and could help in formulation of future products to better manage pain topically.

Conclusion

Topical essential oxygen oil has been shown in clinical studies to be a safe and effective topical analgesic in the treatment of several types of acute and chronic pain syndromes. The exact mechanism of action remains unknown but may relate to the microcirculatory system and possible inhibition of lipid peroxidation or the arachidonic acid cascade or both. While essential oxygen oil is new to the American market, it has been used successfully in Europe for more than a decade. It is a welcome addition to the topical OTC armamentarium of pain relievers in that systemic analgesics are now coming under increasing scrutiny for their potentially toxic effects and, in the case of opioids, because of their potential for misuse. Further study of essential oxygen oil, in particular in other pain syndromes, is warranted.

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