

Oregano Extract Ointment for Wound Healing: A Randomized, Double-Blind, Petrolatum-Controlled Study Evaluating Efficacy

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ABSTRACT

Background: Wound healing is a dynamic and complex process affected by tissue hydration, the presence of bacteria, inflammation, and other variables. Oregano has potent antibacterial, antifungal, antioxidant, and anti-inflammatory properties. Studies of oregano ointment on wound healing are lacking.

Objective: To determine the efficacy of 3% oregano extract ointment on wound healing.

Methods: An investigator initiated, randomized, double-blind, petrolatum-controlled study was performed to determine the effects of oregano ointment on wound healing. Forty patients who underwent surgical excision were enrolled and randomized. Cultures were obtained on day 12 and scars were evaluated using the Patient and Observer Scar Assessment tool on day 12, 45, and 90.

Results: The oregano ointment group had 19 percent of cultures test positive for *Staphylococcus aureus* compared to 41 percent in the petrolatum group. One patient in the oregano ointment group developed a cellulitis compared to three patients in the petrolatum group. The oregano group had a statistically significant improvement over petrolatum in scar color, pigmentation, and pliability.

Conclusion: Oregano extract ointment decreased bacterial contamination and subsequent infection on post-surgical wounds and had equivalent overall scar appearance compared to petrolatum.

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INTRODUCTION

Cutaneous wound healing is a dynamic and complex process that is influenced by multiple variables including the local skin environment. One important variable in epidermal wound healing is the presence of bacteria, because excessive bacterial growth in damaged skin can delay healing.^{1, 2} Topical antibiotic ointments are frequently used in surgical wound/biopsy aftercare protocols.³ However, topical antibiotic ointments are common sensitizers leading to the development of allergic contact dermatitis which limits their use in wound healing.^{3, 4} Ointments containing bacitracin, neomycin, and polymyxin in various combinations are frequently used for wounds. Both bacitracin and neomycin are listed on the top ten most common allergens identified by the North American Contact Dermatitis Group.^{5, 6}

Hydration of the skin is another important variable that can influence wound healing. Studies have shown that maintaining tissue hydration by the application of ointments and occlusive dressings increases epithelial migration and enhances skin re-epithelization.⁷⁻⁹ Pure petrolatum, which is a hydrating and hypoallergenic product, is another frequently used topical agent for wounds, although it lacks antimicrobial properties. Studies have found that

topical antibiotic ointments reduce bacterial infection and enhance wound healing compared to petrolatum or dressing alone,¹⁰⁻¹³ while other studies have found equal infection rates between petrolatum and topical antibiotic ointment.¹⁴⁻¹⁶ Currently, there is in no one standard topical agent used for wound healing, and a need for new, effective topical agents for wound healing exists.

The increasing prevalence of antibiotic resistance highlights the need for new classes of antibiotics.¹⁷⁻²⁰ Moreover, multiple studies have documented the antimicrobial properties of various plant extracts. Oregano is a unique spice herb since it seems to have one of the most potent antibacterial properties along with antifungal, antioxidant, and anti-inflammatory properties.²¹ Many in vitro and in vivo studies have shown oregano (*Origanum vulgare*) to have antimicrobial activity against *Staphylococcus aureus* (*S. aureus*), including methicillin resistant *S. aureus* (MRSA), *Streptococcus haemolyticus*, *Listeria monocytogenes*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Salmonella typhi*; and antifungal properties against *Aspergillus niger* and *Aspergillus flavus*.²¹⁻²⁶ This study was done with the water-soluble fraction of the oregano plant, obtained after distilling the essential oil,²⁷ because the essential oil component may be irritating when used topically.²⁸⁻³² According to

the article by Singletary, "the volatile nature of the components of oregano oils can be irritating to mucous membranes and it is recommended that the oils not be applied topically to mucous membrane at greater than 1% concentrations."²⁸ Also, terpinene, one of the major components of the oregano essential oil, is a hydrocarbon that is classified as a terpene. Terpene was found to be a strong sensitizer,²⁹ and to cause a positive patch test in patients with tea tree oil contact dermatitis.³⁰ We hypothesize that the essential oil-free, water-soluble fraction of oregano would be less sensitizing while retaining the antimicrobial, antioxidant, and anti-inflammatory properties given its high phenolic component.^{33,34}

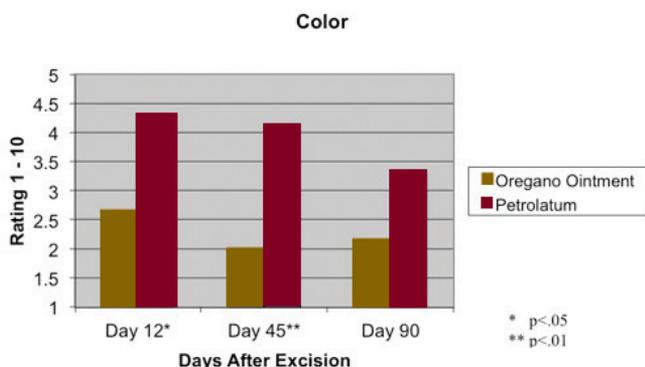
MATERIALS AND METHODS

Institutional review board approval was obtained and study protocol conformed to current ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each patient prior to participation in the study. A single center, investigator-initiated, randomized, double-blind, petrolatum-controlled study was performed to determine the effects of an oregano extract ointment versus petrolatum on wound healing. We used 3% water-soluble oregano extract in petrolatum made from Oregano Natural Preservative (ONP), a patented oregano extract product that has all essential oils removed.²⁷

STUDY DESIGN

Forty adult patients, 18-75 years old, who underwent excisions for treatment of various dermatologic conditions, regardless of this study, were randomized to one of two groups: 1) the oregano ointment, or 2) petrolatum. Excision sites included the trunk and upper and lower extremities, excluding only the legs, head, and neck. Excisions were performed by resident physicians under clean technique, which included clean gloves, sterile instruments and sterile gauze. Chlorhexidine prep was used and followed by local anesthetics with lidocaine with epinephrine. Buried dermal sutures, using a polyfilament, absorbable material, and simple interrupted or running sutures, using a monofilament, non-absorbable material, were used for skin closure.

FIGURE 1. Patient Scar Assessment



Rating scale: 1= normal skin, 10 = worst scar imaginable

After the excision, the study ointment was applied to the excision site by a medical assistant, out of the site of the evaluating physicians, and then covered with a non-occlusive dressing. On day 0 the study ointment was provided to the patient in a concealed container, and they were instructed to apply the ointment twice-a-day to the site and cover it with a non-occlusive dressing. On day 12 +/-2 days, the patients returned for suture removal, a culture of the excision site was taken, compliance with the ointment and adverse reactions were recorded. A physician evaluated the scar using the Observer Scar Assessment Scale, which grades 5 components of the scar: vascularity, pigmentation, thickness, relief, and pliability on a scale of 1-10 with 1 being normal skin and 10 being most severe or the worst scar imaginable.^{35, 36} The patient completed a similar scar assessment questionnaire which had the patients rank itch, pain, color, stiffness, thickness, and irregularity on a similar 1-10 scale. The scar was graded using the same patient questionnaire and Observer Scar Assessment Scale on day 45 and day 90 and adverse reactions were recorded. A two-tailed Student t-test using GraphPad Software was used to analyze the data with an a priori level of 0.05.

RESULTS

Forty patients, 23 females and 17 males, aged 22-72 years old, were enrolled in the study. Four patients dropped out of the study for personal reasons and three patients' culture results were not obtained but were evaluated clinically for infection and scar assessments. The oregano ointment group had three out of 16 (19%) cultures test positive for *S. aureus*, and one out of 16 cultures test positive for methicillin resistant *S. aureus* (MRSA). The petrolatum group had seven out of 17 (41%) cultures positive for *S. aureus*, and no cultures were positive for MRSA. One patient of the 17 patients (6%) in the oregano ointment group was treated clinically for cellulitis. Three patients of the 19 patients (16%) in the petrolatum control group were treated clinically for cellulitis. All four patients with cellulitis had a positive culture result for *S. aureus*.

The average of the Patient and Observer Scar Assessment scores of the oregano and petrolatum groups at day 12, 45, and 90 are shown in Table 1 and 2, respectively. Student's *t*-test was used for statistical analysis of the scar scores. In the patient scar assessment, the oregano ointment group had lower scores, or closer to normal skin than the petrolatum group in color, stiffness, thickness and irregularity (Table 1). By comparison, the oregano ointment group had a statistically significant improvement over the petrolatum group for color on day 12 ($P=0.04$) and day 45 ($P=0.009$, Figure 1). The physician scar assessment showed that the oregano ointment group score was lower or closer to normal skin than the petrolatum group in all five categories: pigmentation, vascularity, thickness, relief, and pliability (Table 2). In the physician scar assessment, the oregano ointment group had a statistically significant improvement over petrolatum in pigmentation on day 12 ($P= 0.0014$), and pliability on day 90 ($P= 0.05$, Figure 2).

No significant adverse reactions were noted in either group. Mild pruritus was noted in five patients in the oregano ointment group and six patients in the petrolatum group. One patient in the oregano group and three patients in the petrolatum group noted mild tenderness each of whom had cellulitis.

DISCUSSION

With the high rate of allergic contact dermatitis to existing topical antibiotics and the increasing prevalence of antibiotic resistance, new classes of antibiotics are needed for wounds. The oregano used in this study was grown from a select oregano clone with high phenolic compounds and then distilled to remove all the essential oil.²⁷ The antimicrobial action of the oregano extract is attributed

mostly to abundant water-soluble phenolic compounds.³³ The leaf extract contains phenolic compounds such as rosmarinic acid, caffeic acid as well as flavonoids including epicatechin or quercetin giving it antioxidant, antimicrobial, antifungal, and anti-inflammatory activity without the irritating and sensitizing chemicals.^{33,34} Removing the essential oil is an important step, because the essential oils have been increasingly reported to cause allergic contact dermatitis.²⁸⁻³² This oregano water-soluble extract has been shown to be effective against gram-positive and gram-negative microorganisms as well as mold and some yeast (data not shown).

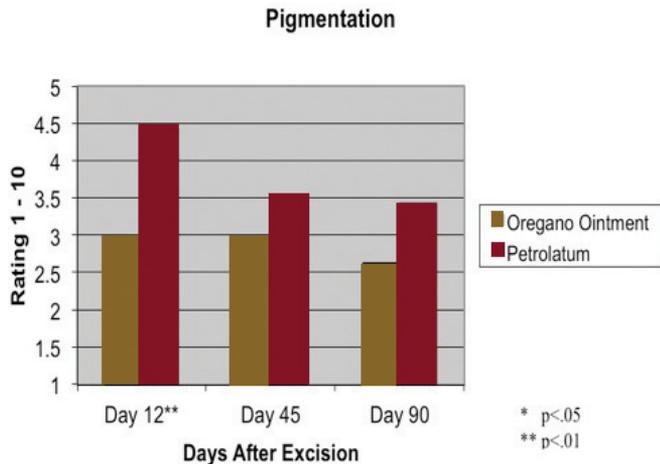
The results of this pilot study demonstrate that oregano extract ointment was an effective antimicrobial ointment for wound healing. The oregano ointment group had fewer positive bacterial cultures for *S. aureus*, 19 percent versus 41 percent, and fewer acute infections, 6 percent versus 16 percent, compared with the petrolatum group. While the petrolatum infection rate appears higher than typically reported in the literature, it is similar to 17.6 percent seen in the petrolatum group in the article by Dire, et al,¹¹ and is limited by the small sample size and inter-resident surgeon variability. Another finding that deserves attention is the high colonization rate seen in the petrolatum group, which indicates a need for further evaluation, but may partially be contributed to the high nasal colonization rates that currently exist in the general population.³⁷ Overall, oregano ointment was effective at reducing bacterial contamination of the excision site at day 12, which resulted in a reduction of acute infections. Although these numbers were not statistically significant, a clinically important trend is observed which highlights the need for larger clinical trials involving water soluble oregano extract ointment on wound healing.

In regards to scar assessment, this study used a validated scar assessment tool known as the Patient and Observer Scar Assessment.^{35,36} Pigmentation in the physician assessment is similar to the color category in the patient assessment. A statistically significant improvement in the oregano group compared to the petrolatum group occurred in both the physician and patient scar assessment of pigmentation and color, which highlights the consistency between the physician and patient scar assessment scores. While all the oregano scores on day 90 were lower (closer to normal skin) in the physician scar assessment, only pliability reached a statistically significant difference. Therefore, the oregano ointment group was essentially equivalent to petrolatum, the current standard, post-operative ointment, in regards to scar assessment.

These results are promising, despite the limitations of a small sample size and a single center. Another limitation of this study is that different resident physicians were performing the excision and thus inter-surgical variability and experience could play a role in the scar outcome and infection rate.

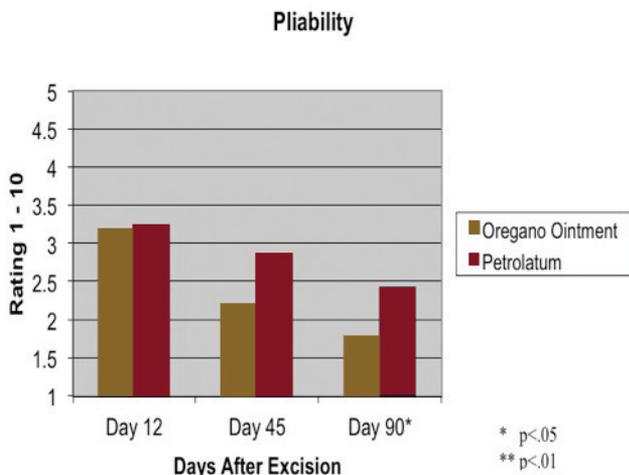
Oregano ointment was well tolerated by the study group without significant adverse reactions. Further large-scale, ran-

FIGURE 2a. Physician Scar Assessment



Rating scale: 1 = normal skin, 10 = worst scar imaginable

FIGURE 2b. Physician Scar Assessment



Rating scale: 1 = normal skin, 10 = worst scar imaginable

TABLE 1.

Patient Scar Assessment							
Treatment	Day 12	Itching	Pain	Color	Stiffness	Thickness	Irregularity
Oregano Ointment	Avg	3.94	2.12	2.64	2.00	2.47	1.87
Petrolatum	Avg	3.53	2.00	4.29	2.47	3.07	2.81
<i>Mean Difference</i>		0.41	0.12	-1.65*	-0.47	-0.60	-0.95
Treatment	Day 45	Itching	Pain	Color	Stiffness	Thickness	Irregularity
Oregano Ointment	Avg	1.73	1.09	2.00	1.36	2.00	1.33
Petrolatum	Avg	1.40	1.07	4.14	2.00	2.20	1.79
<i>Mean Difference</i>		0.33	0.02	-2.14**	-0.54	-0.20	-0.45
Treatment	Day 90	Itching	Pain	Color	Stiffness	Thickness	Irregularity
Oregano Ointment	Avg	1.44	1.00	2.14	1.56	1.67	1.25
Petrolatum	Avg	1.31	1.08	3.33	1.83	2.50	2.25
<i>Mean Difference</i>		0.14	-0.08	-1.19	-0.28	-0.83	-1.00

* $P < 0.05$ ** $P < 0.01$ **TABLE 2.**

Physician Scar Assessment						
Treatment	Day 12	Pigmentation	Vascularity	Thickness	Relief	Pliability
Oregano Ointment	Avg	2.941	2.647	3.294	2.353	3.176
Petrolatum	Avg	4.421	3.053	3.211	2.526	3.222
<i>Mean Difference</i>		-1.48**	-0.406	0.084	-0.173	-0.046
Treatment	Day 45	Pigmentation	Vascularity	Thickness	Relief	Pliability
Oregano Ointment	Avg	3.000	2.727	1.818	2.364	2.182
Petrolatum	Avg	3.533	2.733	2.133	2.800	2.857
<i>Mean Difference</i>		-0.533	-0.006	-0.315	-0.436	-0.675
Treatment	Day 90	Pigmentation	Vascularity	Thickness	Relief	Pliability
Oregano Ointment	Avg	2.625	2.750	1.375	3.250	1.750
Petrolatum	Avg	3.423	3.154	1.846	3.250	2.417
<i>Mean Difference</i>		-0.798	-0.404	-0.471	0.000	-0.67*

* $P < 0.05$ ** $P < 0.01$

domized, controlled trials using oregano water-soluble extract ointment in different concentrations for wound healing are needed. Oregano extract ointment has unique antibacterial, antifungal, anti-inflammatory, and antioxidant properties. In this randomized, petrolatum-controlled study, oregano ointment decreased bacterial contamination and acute infection on post-surgical excision wounds. Oregano extract was well tolerated without significant adverse reactions. Further large-scale, randomized, controlled trials using oregano water-soluble extract ointment for wound healing are needed.

DISCLOSURES

Dr. Daphna Havkin Frenkel is Vice President, and Director of Research and Development for Bakto Flavors, LLC.

Drs. Ragi, Pappert, Rao, and Milgraum have no relevant conflicts of interest.

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