



Prospective, Randomized, Double-Blind, Placebo-Controlled Study on Efficacy of Copaiba Oil in Silicone-Based Gel to Reduce Scar Formation

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ABSTRACT

Introduction: Scars are the end result of a biologic and natural process of wound repair after injury, surgery, acne, illness, burns, and infection. When skin is damaged, a fast and coordinated body response is triggered by four highly integrated and overlapping phases including homeostasis, inflammation, proliferation, and tissue remodeling. Healing of a skin wound may result in an abnormal scar if the balance among these four phases is lost during the healing process. Various topical treatments have been used for their ability to reduce unsightly scar formation. Recently, studies have shown improvement in scar appearance after treating with silicone gels containing natural herbal ingredients. The aim of this study is to evaluate the efficacy of a novel silicone-based gel containing copaiba oil (Copaderm) for prevention and/or appearance reduction of different types of abnormal scars.

Methods: This study was designed as a prospective, randomized, double-blind, placebo-controlled trial involving 42 patients with

abnormal scars, divided into two groups. Each group received either a topical scar formulation consisting of copaiba oil in silicone gel or a placebo gel twice a day for 84 days. Assessments of the scars were performed at 0, 28, and 84 days following the onset of topical application using three methods: a clinical assessment using the Manchester Scar Scale, a photographic assessment to establish before and after treatment improvements, and at the end of the study period, patients completed a final satisfaction questionnaire.

Results: Of the original 42 patients, 32 completed the evaluation. There was a significant difference with respect to the overall score of the Manchester Scar Scale between the two groups from baseline to 84 days ($P < 0.05$). All patients with copaiba oil in silicone gel achieved improvement of their scars, based on overall score at 84 days. A visible scar reduction was observed with photographic assessment. Eighty-nine percent of subjects ($n = 16$) with copaiba oil in silicone gel rated as being satisfied or very satisfied after 84 days of treatment.

Conclusion: Our findings support the hypothesis that copaiba oil in silicone-derivative gel was able obtain significant improvement in color, contour, distortion, and texture for different types of scar through the Manchester Scar Scale analysis. These findings contribute to reducing abnormal scar formation during the healing process.

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Key Summary Points

Why carry out this study?

The association of natural ingredients with silicone-based gels has been shown to be effective in topical therapy for abnormal scar reduction

The current clinical trial evaluated the effectiveness of Copaiba oil associated with silicone gel in reducing the appearance of different types of scars

What was learned from the study?

Copaiba oil in silicone-derivative gel (Copaderm) improves the scarring outcome of abnormal scars and provides a beneficial effect on the scar appearance

The color, contour, distortion, and texture of the scars reduce over time with Copaderm applied twice a day over 84 days

include itching, stiffness, scar contractures, and pain as physical outcomes, and anxiety, mood disturbance, diminished self-esteem, and social ostracism leading to isolation and reduced engagement in society as social and psychological consequences [2, 3].

Various topical treatments have been used for their ability to reduce scar formation [4]. Occlusive dressings containing silicones have successfully been employed as first-line treatment in the prevention of a wide range of scars. Silicone-based products have important advantages compared with other scar reduction therapies as they are a painless non-invasive treatment, have a strong patient compliance, and are easy to apply. Furthermore, silicone-based gels are cosmetically acceptable and exert several beneficial actions for injured skin such as hydration of the stratum corneum, antimicrobial protection, homeostasis of the skin's barrier, and control the synthesis and deposition of collagen during the remodeling phase of skin healing. Recently, studies have shown improvement in scar appearance after treatment with silicone gels containing natural herbal ingredients [5, 6].

In this context, natural products such as plant extracts and essential oils have been beneficial in the development of new products for scar treatment, mainly due to their emollient, moisturizing, antimicrobial, and anti-inflammatory activities [7]. Among the medicinal plants with potential efficacy for improving scar appearance is copaiba oil, an oil rich in terpenic compounds obtained by tapping the trunk of the trees from different species of *Copaifera* L. [8]. Copaiba oil is used in Amazonian traditional medicine, especially as an anti-inflammatory and antimicrobial ingredient for wound healing, and its use has been reported since the sixteenth century [9]. In addition to its application in traditional medicine, studies have demonstrated that copaiba oil is effective in collagen formation and increasing elastic fibers during the healing process. Copaiba oil was also able to increase the concentration of fibroblast and blood vessels of postoperative wounds, demonstrating an improvement of tissue repair after topical application. These findings suggested copaiba oil as a promising adjuvant in

INTRODUCTION

The wound healing process after injury to the skin is complex, with many overlapping mechanisms involved, including inflammation, proliferation, and tissue remodeling. Scars arise after almost every dermal injury. The formation of a scar is a natural and inevitable outcome of mammalian tissue repair that usually forms and becomes visible during the remodeling phase of wound healing [1]. Estimates indicate that each year around 100 million people in the developed world acquire scars following elective surgery and surgery for trauma, with approximately 15% of these cases developing abnormal or unesthetic scars. Excessive scarring can have profound physical, psychological, esthetic, and social consequences. Some of these problems

topical formulations for wound healing, justifying its traditional use [10–14].

However, no study has tested the efficacy of topical copaiba oil in a silicone-based gel to improve the appearance of scars. This is of particular interest because of the potential complementary and synergistic effects of copaiba oil and silicone in scar reduction. The objective of this 84-day, randomized, double-blind, placebo-controlled study was to evaluate the efficacy of a novel silicone-based gel containing copaiba oil for prevention and/or reduction in appearance of different types of abnormal scars.

METHODS

Subject Inclusion and Exclusion Criteria

Forty-two healthy patients of either sex, aged 18–65 years, who consented to enroll in this study were included. Eligible subjects had elevated scars resulting from surgery, cuts, laser procedure, or burns, and/or wounds where the scar age was no more than 120 days (new scars) and located in an area easily accessible for clinical evaluation. Patients with known hypersensitivity or allergy to silicone or any of the ingredients of the treatment; patients who were pregnant or who planned to become pregnant during the study duration; patients who had a medical condition that would prevent normal healing such as diabetes, peripheral vascular disease, peripheral neuropathy, cancer, rheumatological disease, or lupus; patients with scars with an open wound component; and patients using medication(s) and/or cosmetic(s) likely to interfere with study results were all excluded from the study.

Study Design

This prospective, randomized, double blinded, placebo-controlled clinical trial was designed, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. The study was also conducted in accordance with standard operation procedures, the US and international standards of Good

Clinical Practice (FDA regulations 21 CFR for IND studies and FDA guidance E6), and the Declaration of Helsinki concerning medical research in humans. The study protocol and informed consent form were reviewed and approved by an Institutional Review Board (Allendale Investigational Review Board, Old Lyme, CT, USA).

Sample Preparation

The treatment samples consisted of copaiba oil in silicone gel; Copaderm (Medisca Inc, Plattsburgh, NY, USA), a personal scar care product containing a proprietary mixture of silicone polymers and refined copaiba oil along with other ingredients. The content of placebo gel was water, potassium sorbate, ethoxy diglycol, and hydroxyethyl cellulose. Both samples were prepared to be similar in terms of appearance and consistency. Copaderm and placebo gel were also placed in identical dispensers, which were then labeled.

Study Participants and Assessment of Scars

All of the subjects were randomly distributed into two groups. Twenty-one patients for each group received a topical scar formulation consisting of copaiba oil in silicone gel (study group) and a topical hydroxyethyl cellulose gel (control group), twice daily for 84 days. The Manchester Scar Scale (MSS) was recorded at baseline and after 84 days of treatment. The Manchester Scar assessment, described by Beausang et al. [15] in 1998, was used to quantify scar appearance in response to treatment in this clinical study. The scale includes color, contour, distortion, and texture. Each of these parameters is given a score of 1 to 4, with increasing values indicating higher scar severity. Whether a scar is matte or shiny is also recorded, the former scoring 1 and the latter 2 on the overall scale (Table 1). The overall evaluations were calculated by score averages from the scale and subsequently used for the data analysis.

Photographs were also collected at baseline, 28 days, and 84 days using identical camera

Table 1 Manchester Scar Scale (MSS)

Score	1	2	3	4
Color	Perfect	Slight mismatch	Obvious mismatch	Gross mismatch
Matte versus shiny	Matte	Shiny	–	–
Contour	Flush with surrounding skin	Slightly proud/indented	Hypertrophic	Keloid
Distortion	None	Mild	Moderate	Severe
Texture	Normal	Just palpable	Firm	Hard

settings, lighting conditions, and patient positioning (Nikon D300, 13.1 million total pixels, 12.3 million effective pixels) to establish “before” and “after” treatment improvements. At the end of the study period, patients completed a final satisfaction questionnaire (Table 2).

Statistical Analysis

Data analysis was performed using Microsoft Excel 2016 and R i386 3.6.1. Mean changes in parameters within groups were assessed for significance using a paired two-sided *t* test. Mean difference in the improvement of each parameter between test groups was assessed using a

one-sided Welch’s *t* test to account for heteroscedasticity of the sample set. Values for $P < 0.05$ were considered statistically significant. Bonferroni correction was not applied to any parametric hypothesis testing.

RESULTS

Patient Demographic and Clinical Data

At baseline, the subjects were randomly included into one of the two treatment groups. Of the 42 patients initially enrolled, 10 declined after 84 days of treatment. Thus, a total 32 patients (study group, $n = 18$; control group,

Table 2 Patient satisfaction assessment form.

Product evaluation	Scores
1. Color	Unpleasant (1)...(5) Pleasant
2. Smell	Unpleasant (1)...(5) Pleasant
3. Texture	Very sticky (1)...(5) Not sticky at all
4. Irritation	Very irritating (1)...(5) Not irritating at all
5. Ease of use ^a	Very difficult (1)...(5) Very easy
6. Speed of drying	Very slow (1)...(5) Very fast
7. Application ^b	Very difficult (1)...(5) Very easy
8. Feel on skin	Very unpleasant (1)...(5) Very pleasant
9. Overall evaluation	Very dissatisfied (1)...(5) Very satisfied

^a Ease of use: how easy or difficult was it to release the gel from the dispenser

^b Application: how easy or difficult was it to apply and spread the gel onto the scar

$n = 14$) completed the 84-day treatment period and these subjects reported no clinically significant adverse effects. The statistical analysis showed that there was no statistically significant difference in the distributions of gender and age between the test and control groups. Both groups were also well-balanced for Fitzpatrick skin type, race, and location of the scars. The demographic characteristics of each enrolled group are summarized in Table 3.

Clinical Assessment with MSS

The median total MSS scores at each parameter, the overall scores, and the score difference between the baseline and at 84 days are presented in Table 4. The copaiba oil in silicone gel group showed a decrease of the mean scores in all parameters over time from day 0 to day 84. Moreover, the results showed a significant difference with respect to the overall score difference of the MSS between the study and the control groups from the baseline to 84 days ($P = 0.02$). Although there was no significant improvement in matte versus shiny for the study group ($P = 0.16$), this did not affect the relevant reduction (-3.0) of the overall scores at the end of the study compared to the baseline. The results also showed that 100% of the patients with copaiba oil in silicone gel achieved improvement of their scars in the Manchester overall score at 84 days compared to baseline. On the other hand, there were no significant changes in color, matte versus shiny, distortion, texture, and overall scores ($P = 0.10$, $P = 0.34$, $P = 0.44$, $P = 0.44$, and $P = 0.06$, respectively) at 84 days compared to baseline for the control group, and the matte versus shiny score was slightly worse ($+0.08$) after 84 days using placebo gel.

Before and After Pictures

Overall, a visible scar reduction was observed with the use of copaiba oil in silicone gel over time. Before and after photographs of scars of some of the study group patients are shown in Figs. 1, 2 and 3.

Patient Final Evaluation

Overall patient satisfaction was evaluated at the end of the study and 89% of subjects ($n = 16$) with copaiba oil in silicone gel rated as being satisfied and very satisfied with the treatment after 84 days. Eighty-three percent of the patients ($n = 15$) would recommend this gel after completion of the clinical trial.

DISCUSSION

Abnormal scarring, including hypertrophic and keloid scars, is a common inflammatory condition that drives an excessive proliferation of dermal tissue after burns, trauma, and surgical treatment [16]. Silicone gels are commonly used in the topical treatment and prevention of abnormal scars and they possess numerous skin-friendly properties such as biocompatibility, atraumatic removal, extended wear time, repositionability, resistant to microbial growth, and hydrophobicity [17].

Several mechanisms have been proposed as possible modes of action for silicone ingredients. These hypotheses include increased temperature or oxygen tension, inhibitory effect on fibroblast growth, wound hydration, polarization of scar tissue, and modulation of growth factors [18–20]. Clinical evidence supported the use of silicone gel preparations as first-line therapy for excessive scars [21]. Medhi et al. [22] in their study reported differences in response to silicone gel among 36 patients. Decrease in pigmentation, pliability, vascularity, and height was observed after 3 months of using silicone gel on postoperative scars. In the study performed by Chittoria et al. [23] comparing the effect of silicone gel in prevention of hypertrophic scar development in donor site scars showed a significant reduction in overall scores and individual parameters such as vascularity, pigmentation, pliability, and height after 8 weeks of treatment compared to the placebo group.

In recent studies, application of gels combined with natural ingredients have also advanced as one of various efficient nonoperative scar therapies based on various scientific

Table 3 Demographic data of the patients ($n = 42$)

	Study group ($n = 21$)	Control group ($n = 21$)
Gender		
Female	14	14
Male	7	7
Age (mean \pm SD)	44.23 \pm 15.10	49.13 \pm 11.56
Fitzpatrick skin type		
I	0	1
II	9	8
III	7	10
IV	5	2
V	–	–
VI	–	–
Race		
Caucasian	11	14
Black	0	1
Hispanic/Latino	10	06
Location		
Breast	3	1
Chest	3	3
Lip	1	0
Back	2	7
Neck	1	0
Head	2	1
Forearm	1	2
Chin	1	0
Abdomen	1	3
Shoulder	1	2
Knee	0	1
Thigh	2	1
Hand	1	0
Wrist	1	0
Leg	1	0

Table 4 Manchester Scar Scale scores at different time points: mean values \pm standard deviation of mean, overall scores, and score differences from the baseline

	Color	Matte/ shiny	Contour	Distortion	Texture	Total score
Study group						
Mean scores at baseline	3.22 \pm 0.41	1.11 \pm 0.31	2.94 \pm 0.23	2.83 \pm 0.50	2.83 \pm 0.60	12.94 \pm 1.31
Mean scores at 84 days	2.50 \pm 0.50	1.00 \pm 0.00	2.44 \pm 0.89	2.00 \pm 0.66	2.00 \pm 0.58	9.94 \pm 2.12
Score difference baseline/84 day	- 0.72	- 0.11	- 0.50	- 0.83	- 0.83	- 3.00
Mean change*	< 0.05	> 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Control group						
Mean scores at baseline	3.00 \pm 0.47	1.00 \pm 0.00	2.77 \pm 0.42	2.23 \pm 0.42	2.30 \pm 0.46	11.23 \pm 1.12
Mean scores at 84 days	2.5 \pm 0.49	1.08 \pm 0.25	2.08 \pm 0.82	2.08 \pm 0.61	2.15 \pm 0.53	9.85 \pm 2.06
Score difference baseline/84 day	-0.38	0.08	-0.69	-0.15	-0.15	-1.38
Mean change*	> 0.05	> 0.05	< 0.05	> 0.05	> 0.05	> 0.05
Group comparison* (score difference)	> 0.05	< 0.05	> 0.05	< 0.05	< 0.05	< 0.05

Mean \pm SD of MSS at baseline and 84 day follow-up. **P*-value obtained when applying the Student's *t* test (in bold if statistically significant)

**Fig. 1** A Scar on forehead at baseline. B View 28 days after treatment with Copaderm

evidence. Many types of natural products from medicinal plants such as *Allium cepa* extract, pracaxi oil, *Aloe vera*, and, *Centella asiatica* extract have shown activity in scar reduction and show notable advantages in having fewer side effects [5, 24]. Therefore, in addition to widespread uses of surgical therapy, physiotherapy, and pharmacotherapy, there is an enormous need for developing new plant-based

products more efficient than, or synergizing with, the existing ones.

Copaiba oil is widely used in traditional medicine due to its anti-inflammatory, healing, and antiseptic activities, and some authors have shown the effectiveness of copaiba oil in the promotion of wound healing and prevention of abnormal scars [13, 14]. Even with the typical variation in the chemical composition of this



Fig. 2 **A** Acne scar on the back at baseline. **B** View 84 days after treatment with Copaderm

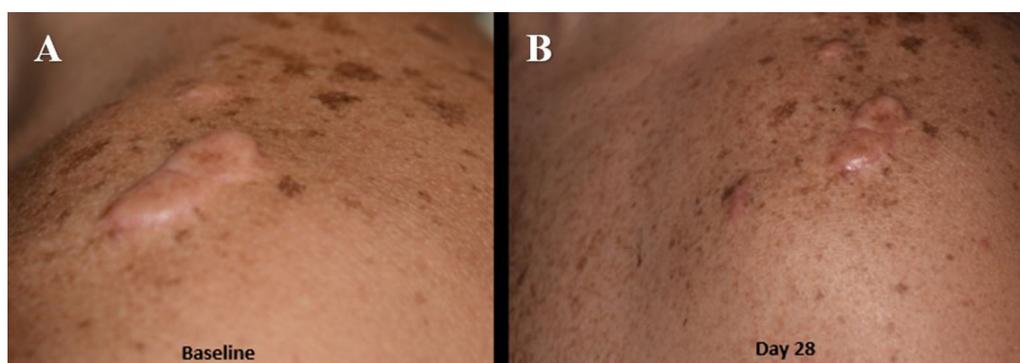


Fig. 3 **A** Keloid on the left shoulder at baseline. **B** View 28 days after treatment with Copaderm

oil, the sesquiterpene β -caryophyllene is the major constituent. This compound represents about 40% of copaiba oil composition and it has been mentioned in literature as a powerful anti-inflammatory, local anesthetic, and anti-microbial agent [25, 26]. Studies show that prolonged inflammation may play a role in excessive scar formation and, as uncontrolled and chronic inflammation of the dermis produces abnormal scars, the use of anti-inflammatory agents can promote faster wound healing with beneficial effects on scar formation [16, 27]. Teixeira et al. [28] demonstrated that copaiba oil resin reduced chronic inflammatory infiltrate and inhibited macrophage activity in

an *in vivo* test using rat's tongues. Although the mechanism underlying the beneficial esthetic effect of copaiba oil on scar appearance is unknown, there is strong evidence that the sesquiterpenes constituents of copaiba oil may reduce scar inflammation, promote progression to the proliferative and remodeling phases, and finally reduce the scar appearance [29].

In face of the benefits from silicone ingredients in scar reduction and the worldwide increase of use of natural products in healing, this clinical trial was the first to demonstrate the effectiveness of topical copaiba oil in silicone-based gel (Copaderm) for the prevention and improvement in the appearance of various scar

types, including hypertrophic, acne and keloid scars. The study compared two groups at 84 days and each group from the baseline to 84 days, during which time all participants were instructed to apply copaiba oil in silicone-based gel or a placebo gel on their scars.

The results demonstrated that the application of copaiba oil in silicone-based gel two times per day achieved beneficial improvement in appearance of new scars after 84 days when compared with a placebo gel. Characteristics of color, contour, distortion, and texture of the scars showed significant score reduction (-0.72 , -0.5 , -0.83 , and -0.83 , respectively) from the baseline to 84 days, as well as a significant difference ($P < 0.05$) between study and control groups overall scores in the Manchester Scar Scale.

Other authors have also gone further investigating the use of silicone gel and have found similar benefits in the combination of silicone derivatives plus plant-based ingredients in the treatment and reduction of scars. Jenwitheesuk et al. [30] observed improvement in pain, itch, and pigmentation of scars after using a combination of a silicone gel and onion extract for hypertrophic scars over a treatment period of 12 weeks in comparison with a placebo group. In another clinical trial conducted by Nestor et al. [5], a silicone gel containing pracaxi oil was effective as an onion extract gel for improving the appearance of hypertrophic post-surgical scars after 12 weeks of treatment.

Our findings support the hypothesis that copaiba oil in silicone-derivative gel (Copa-derm) can improve the scarring outcome of abnormal scars and it provides a beneficial effect on the scar appearance of the subjects. In addition, the majority of patients in the study group (89%) responded that they were satisfied using the patient self-assessment that included allergic reaction, product appearance, overall comfort, speed of drying, application, feel on skin, and overall satisfaction. It is compelling to note that, based on this satisfaction assessment, 83% of these patients would recommend Copaderm after 84 days of treatment. The before and after photograph comparisons combined with the patients' assessment also provide good evidence that the application of copaiba

oil in silicone-based gel for 84 days ameliorated the appearance of different type of scars in the study group.

To our knowledge, this prospective study represents the first evaluation of the scar reduction efficacy following copaiba oil in silicone-based gel application. Despite the fact that this study has reported promising results, it has some limitations. Most important is the small number of subjects for each group ($n = 21$) and the fact that only Manchester Scar Scale has been used to assess the scar parameters during the treatment. Although this scale has been validated and is commonly used for scar care products evaluation, it is still subjective. Because this study population was relatively small, it would be advisable to study the effectiveness of topical copaiba oil in silicone-based gel on a larger scale. A comparative study with silicone gel and other plant-based scar reduction products would be another apt comparison.

CONCLUSION

In conclusion, this study demonstrates that copaiba oil in silicone-based gel is able obtain significant improvement in color, contour, distortion, and texture for different types of scar through the Manchester Scar Scale analysis. These findings contribute to reduce the abnormal scar formation during the healing process. There were no side effects found with Copaderm, and patient overall evaluation and compliance were satisfactory. Further research is needed to identify the processes responsible for the development of these beneficial improvements more precisely.

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Compliance with Ethics Guidelines. The study protocol and informed consent form were reviewed and approved by an Institutional Review Board (Allendale Investigational Review Board, Old Lyme, CT). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the USA and international standards of Good Clinical Practice (FDA regulations 21 CFR for IND studies and FDA guidance E6).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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