Laser-Assisted Delivery of Vitamin C, Vitamin E, and Ferulic Acid Formula Serum Decreases Fractional Laser Postoperative Recovery by Increased Beta Fibroblast Growth Factor Expression

Jill S. Waibel, MD,[1*] Qing-Sheng Mi, MD, PhD,[2] David Ozog, MD,[3] Le Qu,[4] Li Zhou, MD,[2] Ashley Rudnick, BS,[1] Firas Al-Niaimi, MSc, MRCP, EBDV,[5] Julie Woodward, MD,[6] Valerie Campos, MD,[7] and Serge Mordon, PhD[8]

[1]*Miami Dermatology and Laser Institute, 7800 SW 87th Avenue, Suite B200, Miami, Florida 33173*

[2]*Hesnry Ford Immunology Program, Departments of Dermatology and Internal Medicine, Henry Ford Hospital, 1 Ford Place, Detroit, Michigan 48202*

[3]*Henry Ford Immunology Program, Henry Ford Hospital, 3031 W Grand Blvd., Detroit, Michigan 48202*

[4]*Henry Ford Immunology Program, Department of Dermatology, Henry Ford Hospital, 1 Ford Place, Detroit, Michigan 48202*

[5]*Sk:n Clinic, 144 Harley Street, London, UK*

[6]*Duke University, 2351 Erwin Rd., Suite 3802, Durham, North Carolina 27705*

[7]*Clínica Valéria Campos, Jundiaí, São Paulo, Brazil*

[8]*INSERM U1189, INSERM, 1 Avenue Oscar Lambret, Lille, France*

Background and Objective: Laser-assisted drug delivery is an emerging technology to achieve greater penetration by existing topical medications to reach desired targets in the tissue. The objective of this research was to study whether laser-assisted delivery of Vitamin C, E, and Ferulic immediately postoperatively of fractional ablative laser could improve wound healing. Secondary objectives were to evaluate the potential molecular markers involved in this wound-healing process.

Study Design/Material and Methods: A double blinded, prospective, single center, randomized split face trial of Vitamin C, E, and Ferulic topical formula #740019 to decrease postoperative recovery time in fractional ablative laser resurfacing for photo damage. Fifteen healthy men and women of ages 30–55 years were treated with the Vitamin C, E, and Ferulic acid serum to one side of face and vehicle to the other side of face, within 2 minutes immediately after fractional ablative CO_2 laser surgery and daily during the healing process. Patients were evaluated daily on days 1–7 using photographs, patient questionnaires, and molecular evaluation.

Results: Clinically, postoperative Vitamin C, E, and Ferulic delivery resulted in decreased edema versus vehicle on postoperative day 7 and decreased erythema versus vehicle on postoperative days 3 and 5. Molecularly, the expression of basic fibroblast growth factor (bFGF) was significantly increased at day 5 on the lesion treated with Vitamin C, E, and Ferulic acid serum compared to vehicle control on the other side.

Conclusion: This is first study to show that Vitamin C, E, and Ferulic acid correlate with more rapid wound healing post-fractional ablative laser. Elevated bFGF could be involved in the Vitamin C, E, and Ferulic acid-induced rapid wound healing. Lasers Surg. Med.

Key words: drug delivery systems; wound healing

INTRODUCTION

Ablative fractional resurfacing has become a powerful tool for facial skin rejuvenation. In our busy society, postoperative downtime is a major factor for patients when considering esthetic procedures.

Fractional lasers were developed within the last decade to treat rhytids [1,2]. Non-ablative fractional lasers were first discovered and only function to coagulate collagen. In 2008, more robust fractional ablative lasers were introduced, which vaporize thin columns in the epidermis and dermis in a fractional pattern. The depth of these zones is determined by the laser fluence. Because the wounds are so small (120–300 μm in diameter), there is a rapid healing response with a unique molecular healing cascade and prolonged neocollagenesis [3]. These microscopic vertical

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*Correspondence to: Jill S. Waibel, MD, Miami Dermatology and Laser Institute, 7800 SW 87th Avenue, Suite B200, Miami, FL 33173.

E-mail: jwaibelmd@miamidermlaser.com

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channels of ablation in the skin are surrounded by variable thin layers of coagulated tissue and additionally by relatively spared, healthy tissue.

Using fractional ablative lasers on the stratum corneum, epidermis, and dermis enhances penetration of topical medications and allows a new doorway for new medications to get into the skin. Fractional laser-assisted delivery enables physicians to uniformly distribute drugs in microscopic channels. Fractional laser creates a conduit allowing a drug to bypass the epidermal barrier. The creation of these channels provides an accessible pathway for topically applied drug molecules to freely traverse the epidermal layer.

Laser-assisted drug delivery is an evolving technology with potentially broad clinical applications. Multiple previous studies demonstrated that laser pretreatment of skin could increase the permeability and depth of penetration of topically applied drugs and other molecules [4–10].

Almost every species of animal is capable of converting glucose into ascorbic acid. However, humans and guinea pigs lack a critical enzyme and are unable to produce ascorbic acid independently. Therefore, humans must consume the entirety of their Vitamin C needs. Low levels of Vitamin C lead to symptoms of scurvy. One of the cutaneous signs of scurvy is poor wound healing [11]. The subject of using Vitamin C and E to aid in wound healing has been shown as early as 1941 [12]. Vitamin C is an essential cofactor for the biosynthesis of collagen, crucial for prolyl hydroxylase and lysyl hydroxylase enzymes, and thus plays an undeniable role in aiding the process of wound healing [13–16]. Other vitamins, including Vitamins A, E, and K, are also important for proper wound healing [17–19].

When properly formulated with pure Vitamin C (L-ascorbic acid), at an acidic pH (<3.5), and containing a significant concentration of Vitamin C (10–20%), the serum has been shown to penetrate the epidermis and deliver a substantial amount of Vitamin C into the skin [20]. Under normal daily conditions, the Vitamin C, E, and Ferulic acid serum is able to supply the skin with a significant amount of antioxidants needed for optimal skin health. However, the injury induced by the fractional laser substantially depletes cutaneous antioxidants to a degree well beyond normal daily conditions. For this reason, it may be impactful to deliver a greater amount of Vitamin C, deeper into the skin, in order to promote proper wound healing. An added benefit of applying the antioxidant serum with a low pH is the ability to inhibit the proliferation of *Candida albicans* infections following the laser treatment.

A study simultaneous performed at another clinical site and presented at the 2012 ASLMS annual conference demonstrated that the average duration of side effects resolved 2 days earlier when the topical Vitamin C, E, and Ferulic acid serum was applied immediately post-fractional non-ablative laser treatment [21]. Our current work investigated whether fractional ablative laser-assisted delivery of the Vitamin C, E, and Ferulic acid serum is an effective strategy to increase the topical uptake of the antioxidants to assist in cutaneous repair, and gather data regarding the potential mechanism involved.

We prospectively evaluated the efficacy of a 15% Vitamin C, 1% Vitamin E, and 0.5% Ferulic acid serum in improving postoperative wound healing by evaluating the decrease in downtime and molecule markers, after the fractional ablative laser resurfacing procedure, in a photodamage split-face model. We chose this formulation due to its high concentration of Vitamin C, stabilized by Ferulic acid and of a lipophilic base due to the presence of Vitamin E.

MATERIALS AND METHODS

Subject Population

Fifteen subjects exhibiting moderate photodamage (Glogau scale 3) were randomized into this prospective IRB-approved study. Written informed consent was obtained from each patient. Exclusion criteria were pregnancy, breastfeeding, and use of oral retinoids 6 months prior to treatment, active infection, or lesions suspicious for malignancy. The first 15 subjects to meet inclusion criteria were enrolled in the study and zero patients dropped out from the study.

Study Design

This was a prospective, single-arm, split-face, double-blind, controlled, pilot study conducted to determine the effect of fractional ablative laser followed by immediate topical 15% Vitamin C, 1.0% Vitamin E, and 0.5% Ferulic acid serum application to improve postoperative wound healing. Prior to the procedure, each subject received a topical anesthetic gel containing 20% benzocaine, 8% lidocaine, and 4% tetracaine. Each subject received full face treatment with a fractional ablative carbon dioxide laser (Lumenis Ultra Pulse ActiveFX Santa Clara, CA). The depths that were used ranged from 66 to 112 μm (90–125 mJ), with size 10 and shape 2, with 68% density in a stamping technique used by the primary investigator. The exact setting was determined based on the skin type and the degree of photodamage of the subject. Immediately following laser treatment was a 7-day postoperative skin care regimen of daily application of a topical formulation of Vitamin C, E, and Ferulic acid on one side of face and vehicle on the other. The sides of the face to receive active product versus vehicle were randomized prior to performing the experiment and both patient and treating physicians were blinded. The initial dosage of the Vitamin C, E, Ferulic acid serum was applied at four to five drops dispersion within 2-minutes post-laser treatment, this topical formulation was applied directly into the fractional ablative tunnels.

Test Formula Composition

The active formulation was composed of l-ascorbic acid, alpha-tocopherol, Ferulic acid, water, ethoxydiglycol, propylene glycol, glycerin, laureth-23, phenoxyethanol, triethanolamine, panthenol, and sodium hyaluronate.

TABLE 1. Patient Questionnaires Given to Subject to Document Healing Process for Each Side of Face

	Active: CE Ferulic formula # 740019	Placebo formula #740019 28
Day 1		
Day 2		Patient states that this side burns more than the other side after applying serum. Patient still has minor discomfort
Day 3	Patient has less burning today after applying serums. Patient has minor swelling and little pain	Patient has less burning today after applying serums. Patient has minor swelling and little pain
Day 4		This side tingles for about 1 min when applying serum
Day 5	This side looks better	
Day 6	No comment	No comment
Day 7	No comment	No comment

The vehicle formulation was composed of water, ethoxydiglycol, propylene glycol, glycerin, laureth-23, phenoxyethanol, triethanolamine, panthenol, and sodium hyaluronate.

Posttreatment Care

After the fractional laser procedure, the treatment areas were cooled with ice towels for 10 minutes. Patients were also directed to apply a physical sunscreen and avoid sun exposure while the study was in progress.

Clinical Assessment

To assess postoperative wound healing, four blinded investigators evaluated photographs that were taken at baseline and every 2 days for 1 week following the laser therapy session. Photographs were obtained using identical camera settings, lighting conditions, and patient positioning (Nikon D300, 13.1 million total pixels, 12.3 million effective pixels). These photographs were subsequently evaluated for improvements in edema and erythema using a quartile scale. The quartile scale consisted of overall improvement in edema and erythema, each day blinded investigators rated edema and erythema with scale 0 (no edema/erythema), 1 (mild edema/erythema), 2 (moderate edema/erythema), 3 (severe erythema or edema). Edema and erythema were graded separately. To assess the postoperative downtime, six blinded investigators evaluated photographs to estimate a reduction in downtime by reviewing patient photographs and patient questionnaires (Table 1). These blinded investigators reviewed photographs to evaluate the "day patient could return to work and social activities."

TaqMan Real-Time RT-PCR

We have analyzed many molecular pathways along with biomarker analysis such as biomarkers for protein-coding genes Col 1, Col 3, TGF-b1, TGF-b2, TGF-b3, MMP-1 (collagenase 1), MMP-13, bFGF. We have also tested molecular pathways and biomarkers for non-protein-coding genes miRNA biomarkers by miRNA arrays. After analyzing all the given markers, there was a statistical significance with bFGF that was elevated on the CE Ferulic side compared to the Placebo side. Many growth factors regulate skin physiology, but one in particular, fibroblast growth factor-2 (FGF-2, also referred to as FGF-b), has a wide activity spectrum. In skin, FGF-2 can promote fibroblast cell proliferation, increase the synthesis of matrix macromolecules, including dermal glycosaminoglycans (GAG), hyaluronan (hyaluronic acid, HA) by stimulating the gene expression of hyaluronan synthases, and lastly contributes to the wound-healing process by stimulating fibroblast proliferation and by inhibiting the expression of MMP-1 (collagenase-1). This is monumental finding to see a clinical trend of wound healing with one molecular marker responsive for wound healing on the CE Ferulic Acid aide only. Five patients were randomly chosen for preauricular biopsies at baseline, 5 days and 3 months post-laser treatment (Fig. 1). Total RNA was isolated from the skin biopsies before and after treatment at day 5 and 3 months using the mirVana miRNA isolation kit (Ambion, Austin, TX) according to the manufacturer's specifications. Reverse transcription reactions were performed using

Fig. 1. Grid used to take preauricular punch biopsies in a subset of five patients.

Fig. 2. Split face photo of patients at day 5 after fractional ablative laser and daily application of CEF.

high-capacity cDNA reverse transcription kits (Applied Biosystems, Foster City, CA). The TaqMan primers for Col1A1, TGF-beta1, TGF-beta3, MMP-1, MMP-13, and bFGF were ordered from Applied Biosystems. Results were obtained from the average measured in triplicate and normalized to a control gene GAPDH. Fold changes were generated by calculating 2-ΔΔCt.

Statistics

RT-PCR data was analyzed by the paired Student *t*-test using GraphPad Prism 5.0. Differences with a $P < 0.05$ were considered significant.

RESULTS

Overall

Trend data analysis suggests that postoperatively after ablative fractional laser, Vitamin C, E and Ferulic acid delivery resulted in decreasing edema versus vehicle on postoperative day 7 ($P > 0.05$) and decreased erythema versus vehicle on postoperative days 3 and 5 ($P > 0.05$) (Figs. 2–4 and Table 2). While the results did not yield a statistically significant difference, this may be explained by the limited patient population and substantial variability in individual response. Larger studies are needed to confirm this initial observation. The blinded investigators felt patients could return to both work and social activities at day 5 (Fig. 5). Typically there is 7–10 days of downtime after fractional ablative laser treatment.

To further investigate the potential mechanism involved in Vitamin C, E, and Ferulic acid serum-mediated wound healing, we analyzed the gene expressions of Col1A1, TGF-beta1, TGF-beta3, MMP-1, MMP-13, and bFGF, which are involved in wound-healing processes, at day 0, day 5, and 3 months after treatment. We did not find any gene expression change in Col1A1, TGF-beta1, TGF-beta3,

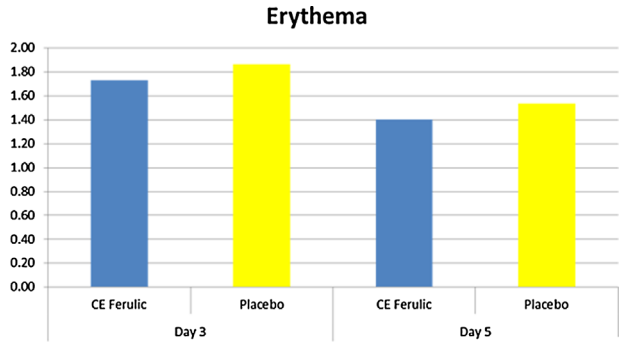

Fig. 3. CE Ferulic acid decreasing erythema in patients.

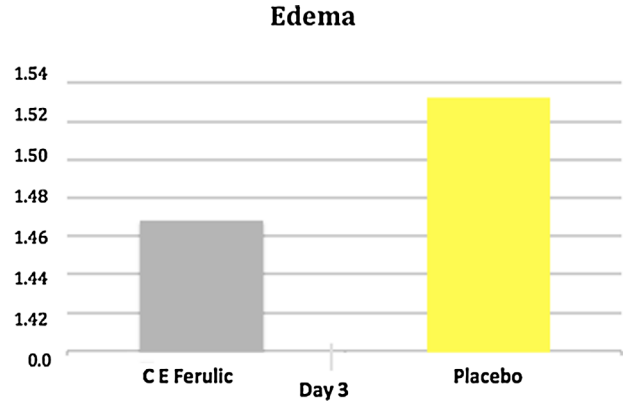

Fig. 4. CE Ferulic acid decreasing edema in patients.

TABLE 2. Statistical Analysis With *P*-Values of Improvement in Healing Time From Days 1 to 7

	CEF serum 740019			Placebo 740019 28	
	Time point	Mean ± SD	Mean % change from baseline	Mean ± SD	Mean % change from baseline
Edema	Baseline	0.4 ± 0.8		0.4 ± 0.8	
	Day 1	1.5 ± 0.8	Significant*	1.5 ± 0.8 *	Significant
	Day 3	1.5 ± 0.8	Significant	1.5 ± 0.8	Significant
	Day 5	1.5 ± 0.5	Significant	1.4 ± 0.5	Significant
	Day 7	0.8 ± 0.6	Not significant	0.9 ± 0.6	Not significant
Erythema	Baseline	0.5 ± 0.9		0.5 ± 0.9	
	Day 1	1.7 ± 0.7	Significant	1.9 ± 0.6*	Significant
	Day 3	1.7 ± 0.7	Significant	1.9 ± 0.6	Significant
	Day 5	1.4 ± 0.6	Significant	1.5 ± 0.6	Significant
	Day 7	1.5 ± 0.7	Significant	1.4 ± 0.8	Significant

Significant implies significant improvement, compared to baseline $P < 0.05$.
*Significant increase compare to baselines.

MMP-1, and MMP-13 after treatment (data not shown here). Previously, we have reported significantly reduced bFGF expression after laser treatment [22]. Consistent with these previous observations, we found a reduction of bFGF expression at 5 days and 3 months posttreatment on the control side (Fig. 6). Interestingly, there is no significant reduction in expression of bFGF at day 5 and 3 months on the side where Vitamin C, E, and Ferulic acid serum was applied (Fig. 6). The side of the face applying the vehicle formula did demonstrate a statistically significant reduction in bFGF at both the day 5 and 3-month time points.

DISCUSSION

The use of fractional ablative lasers to deliver bioactive agent(s) to a patient via channels of predetermined depth, into cutaneous tissue, has wide clinical implications. Small fractional ablative channels provide a means through the barrier function of the skin, allowing direct local delivery into the body. Laser devices have a significant benefit in being tunable so as to control the penetration to a desired tissue depth in an organ. This technology platform uses fractional lasers to predictably disrupt the barrier properties of the skin, creating deep channels that allow for the delivery of cellular materials and agents through the disrupted barrier.

Upon injury to the skin, a set of complex biochemical events takes place in a closely orchestrated cascade to repair the damage. Clinical guidelines generally advise that topical products should be avoided during the first week of recovery. However, incorporating a topical product may aid the wound-healing process and minimize the posttreatment downtime. This is the first study to show Vitamin C, E, and Ferulic acid correlate the clinical effect of wound healing with a specific molecular mechanism of action, increases clinical healing in patients during the initial days after the laser induced injury (days 3–5, Fig. 2).

The mechanism by which Vitamin C, E, and Ferulic acid treatment improves wound healing is presently unknown. While both Vitamin E and Ferulic acid have some antioxidant effects, it is mainly the high concentration of Vitamin C that has shown to have significant antioxidant effects with increasing concentrations. It is plausible that there might have been some synergistic effect, but the concentrations of Vitamin E and Ferulic acid are relatively low and are predominantly added to aid stability and

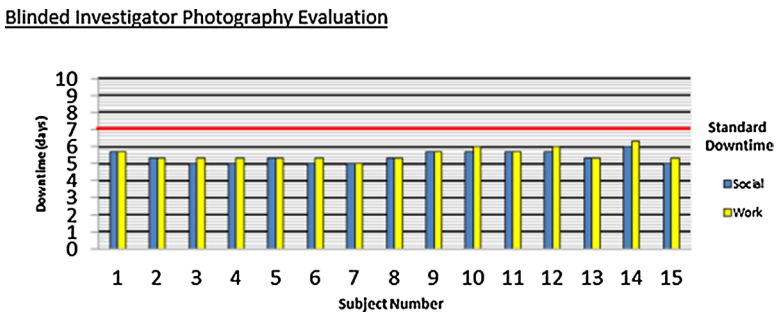

Fig. 5. Blinded investigators photography evaluation on when patients can return to daily activities.

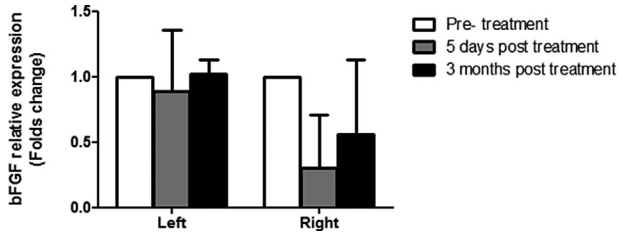

Fig. 6. CE Ferulic increasing bFGF (beta fibroblast growth factor).

lipophilicity of the formulation. We hypothesize that Vitamin C is mainly responsible for the wound-healing improvements. We have analyzed some candidate genes including Col1A1, TGF-beta1, TGF-beta3, MMP-1, MMP-13, and bFGF that are involved in wound-healing processes. We have found that Vitamin C, E, and Ferulic acid treatment can block laser treatment-induced downregulation of bFGF in the skin. bFGF is a glycoprotein, which is widely used in treating wounds and ulcers [23]. Recent study has shown that bFGF application following laser photocoagulation might have protective, repairing, and wound-healing effects on the retina [24]. Furthermore, the factor that preincubation by both bFGF receptor blocker and anti-bFGF antibody significantly decreases proliferative activity in both adult and fetal skin fibroblasts further suggests that bFGF plays very important roles in wound healing. Thus, Vitamin C, E, and Ferulic acid treatment may improve wound healing through block of downregulation of bFGF by laser treatment. However, the detailed signaling pathway involved in upregulation of bFGF by Vitamin C, E, and Ferulic acid treatment needs to be further studied. While it is plausible that both Ferulic acid and Vitamin E may have some antioxidant effects, we believe that the main effect is exerted through the action of Vitamin C. Studies have shown the increased antioxidant action by the use of higher concentrations of Vitamin C, with a constant concentration of Ferulic acid [20,25].

Overall, the formula of Vitamin C, E, and Ferulic acid is well tolerated immediately post-fractional ablative laser. Initial data review (physician, patient) show trends of decreasing downtime 24–48 hours for fractional ablative laser. Even though downtime data did not reach a level of statistical significance, due primarily to the limited subject population, the data gathered as part of this study add to our continued investigation of optimal post-laser care. Analysis of molecular data revealed that the topical serum formulation may protect or stimulate bFGF, which in turn increases fibroblast activity to help repair the wound damage in initial days after the laser-induced injury. These results contribute to a potentially new understanding of the wound-healing mechanism involved in ablative laser surgery. This insight may help explain the exhibited clinical trends of decreasing postoperative downtime 24–48 hours with ability of patients to return to work and social life more quickly. In our study, we did not observe any cases of irritancy or dermatitis due to the use of the topical formulation. This has largely been consistent with its use outside of this study in our clinic (JW). The ablated columns of tissue with the concomitant compromise of the stratum corneum barrier did not seem to potentiate any irritancy. The formula of Vitamin C, E, and Ferulic acid is composed of an aqueous-based vehicle with little to no ethanol. Furthermore, Vitamin E has a lipophilic base, which together with the other ingredients, glycerin and sodium hyaluronate, have a humectant effect on the skin leading to increased hydration [25]. Although allergic contact dermatitis (ACD) and irritated contact dermatitis (ICD) are a major concern after laser resurfacing, this particular compound has been shown to improve wound healing without adverse event of dermatitis. Additional studies are needed to validate this observation.

This is the first study to show that Vitamin C, E, and Ferulic acid correlates the wound healing clinical effect seen in patients with a specific molecular mechanism of action. Upon injury to the skin, a set of complex biochemical events takes place in a closely orchestrated cascade to repair the damage. Vitamin C, E, and Ferulic acid may have wider implications for all human wound healing and change the paradigm of postoperative laser resurfacing patient care.

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