Abstract

Background: Skin rejuvenation can be achieved with minimally invasive treatments using energy-based devices that feature reduced side effects and downtime. Post-treatment care is key to minimize any potential side effects and skin reactions such as erythema, dryness, or dyschromias.

Objective: The objective of this study was to evaluate the efficacy and patient satisfaction of a novel carboxytherapy gel mask compared with petroleum-based lanolin-containing ointment to accelerate wound healing facial post-nanofractional radiofrequency treatment.

Methods and Materials: Ten subjects were enrolled in this pilot, prospective, randomized, single-blind study and randomized into two arms. One arm received one nanofractional radiofrequency treatment with ointment right after and four consecutive days of ointment applications twice a day, while the second arm followed this regimen with a carboxytherapy gel mask application right after and four consecutive days after treatment. Investigator, safety and patient assessments were conducted at 24 hrs and one-week post treatment. Safety was monitored throughout. The primary endpoint was defined as the degree of investigator global assessment (IGA) in photodamage, pigmentation, and wrinkles using standardized photographs. Secondary endpoints included investigator-rated degree of erythema, edema, crusting, exudation, percentage healing, improvement of skin quality and patient satisfaction.

Results: Nine patients completed the study. There was improvement of one degree in IGA for photodamage, pigmentation and wrinkles in all patients using the carboxytherapy gel mask at the one week followup. Blinded investigator ratings showed significant improvement of dryness, erythema, edema, crusting, and percentage healing at the 24 hr

follow up, with all patients remaining the same a week post treatment. All patients in the carboxytherapy group were satisfied with the treatment and had no adverse effects. Three patients in the petroleum-based lanolin-containing group experienced mild edema and acne breakout that resolved two weeks after treatment.

Conclusion: Carboxytherapy delivered via a gel mask after skin rejuvenation procedures is a safe and effective strategy to improve clinical outcomes and reduce post-treatment side effects.

Introduction

Increased patient demand for minimally invasive effective skin rejuvenation treatments that have no downtime, along with innovation in the realm of energy-based devices has led to the development of a plethora of technologies that can decrease photodamage and wrinkles, and improve skin quality. By harnessing ultrasound, laser/light, or radiofrequency energy and targeting the epidermal and dermal skin layers, these devices mediate epidermal turnover, dermal remodeling and collagen/elastin production. Radiofrequency devices for skin rejuvenation are notably popular, as they can have clinical effects in all skin types, as they operate in a chromophore-independent manner. While one of the first generation of radiofrequency devices was used mainly for skin tightening, there are now several iterations of radiofrequency devices depending on their electrode configuration (monopolar, bipolar, multipolar, multi-generator), something that has also expanded their applications. The latest generation of radiofrequency devices is the nano-fractional radiofrequency device (Venus Viva™, Venus Concept, Toronto, Canada). This technology offers precise depth penetration and consistent selection dermal heating as well as controlled coagulation and ablation ability in comparison to other radiofrequency devices. The energy is delivered through 160 pins per tip (62 mJ per pin) and a smaller footprint per pin (150x20 Microns), which results in micro wounds, efficient skin resurfacing, and minimal downtime. Peer-reviewed publications have demonstrated the clinical efficacy of this device in treating striae, acne scars, wrinkles, and skin rejuvenation. [1-3]

Despite the reduced downtime and favorable safety profile, there are some side effects with this treatment, such as erythema, edema, and occasionally hyperpigmentation, that typically resolve within a week. Any means to reduce the time and severity of patient

downtime translates into improved experience, patient satisfaction that will ultimately encourage the patient to repeat the treatment.

Post-treatment care typically comprises of a dressing or ointment that can achieve full contact with the skin such as Aquaphor (Beiersdorf Inc, Wilton, CT, USA) or Vaseline (Unilever Inc, Englewood Cliffs, NJ, USA). However, these ointments do not necessarily reduce the downtime, in fact they have been associated with prolonged erythema, and reactions such as contact dermatitis. Moreover, they are occlusive agents, and their application does not guarantee uniform coating of the injured skin. Irregularities due to exposed skin can increase post-treatment dryness, irritation and skin crusting. Thus, the quest for an improved offering after minimally invasive aesthetic procedures remains and an ideal option would be a topical, breathable, semi-fluid product that allows wound healing, accelerates resolution of inflammation, acts as a sterile physical barrier and maintains the skin surface moist and hydrated.

Carboxytherapy, that refers to the transcutaneous delivery of CO2, has been used therapeutically as it increases vasodilation, circulation, enhances of blood supply and regulates local tissue metabolism. [4]

In aesthetic dermatology, it has been frequently used for the treatment of cellulite, alopecia, periorbital hyperpigmentation and skin rejuvenation. [5-18]

While carboxytherapy is traditionally applied using subcutaneous injections, a novel delivery method of carbon dioxide has been developed that comprises a gel mask that can be applied topically without the need of injections.

In this study the CO2Lift Gel Mask was used to compare the delivery of carbon dioxide to the skin versus an ointment and its subsequent ability to decrease patient's post-treatment downtime after nanofractional radiofrequency treatment.

Materials and Methods

Device Description

Venus Viva™ works with tiny pins that safely deliver heat via NanoFractional Radio Frequency through the skin's surface by creating tiny micro-dermal wounds. CO2 Lift Gel mask (Lumisque, Weston, FL) is composed of a mixture of magnesium carbonate gel and a gluconolactone gel, followed by immediate application of the mixture to the desired treatment area.

Study Design.

This was a single-center, prospective, randomized, pilot study to assess the safety and effectiveness of CO2 lift carboxytherapy gel mask as a post- nanofractional radiofrequency treatment to decrease patient's post-treatment downtime in healthy female subjects. This study was conducted in accordance with the principles of the Declaration of Helsinki, current GCP guidelines, and IRB approval. Informed consent was obtained from all subjects prior to study participation. All subjects received one nanofractional radiofrequency treatment. Immediately post treatment, 5 out of the 10 enrolled subjects received application of CO2Lift gel mask and the other 5 subjects received application of Aquaphor. Subjects applied the CO2lift gel mask or Aquaphor for three additional days.

Subjects

10 subjects, 25-60 years of age with Fitzpatrick skin types (I-VI) with moderate signs of facial aging and moderate photo damage (hyperpigmentation and/or sunspots) were enrolled. Subjects had to agree not to have any procedures affecting facial wrinkles or skin quality (ex. microdermabrasion, peels, acne treatments, filler, botulinum toxin, radiofrequency, laser, IPL, ultrasound) for the duration of the study. Exclusion criteria

included pregnancy, significant systemic illness; past or current, illness localized in area of treatment, therapies or medication that may have interfered with the treatment or healing process, recent surgery in treatment area, and acute or chronic infection in the area. Subjects were required to use an acceptable birth control method.

Treatment

Prior to treatment, the distal part of the applicator was cleaned and fitted with a new 160 pin tip for each patient. Treatment consisted of a single pass over the designated area creating a stamped imprint in a shape and intensity depending on energies.

Photography

Standardized photographs of the face will be taken at 0°, 45° and 315° angles using the Visia® CR system (Canfield Imaging Systems, Fairfield). For each angle, a set of five different photographs will be taken including non-polarized, cross-polarized and parallel-polarized white light as well as UV light images.

Assessment and Outcomes

Primary outcome measures were investigator global assessment (IGA) of photoaging, pigmentation and wrinkles at day 1 and 7 after treatment by blinded investigators. The IGA scale is a 5-point scale from none (0) to severe (4). Additionally, a 10-point scale (0 not improved, 10 extremely improved) that covers radiance, pore size, erythema, pigmentation, smoothness, luminosity, skin complexion, skin tone, and skin clarity as individual parameters were used for investigator and subject ratings of skin quality at day 1 and 7 after treatment. Subject satisfaction with treatment was assessed on a 4-

point scale (0, very satisfied to 4, very dissatisfied). Cosmetic efficacy and ease of use was also assessed with relevant questionnaires.

Investigator tolerability assessments was performed at all visits and included dryness, scaling, edema and erythema from a scale of 0 to 3 (none, mild, moderate and severe).

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, version 22, IBM, Armonk, NY). Quantitative data is presented as mean, standard deviation (SD), and/or range, while qualitative data is presented as percentage (%).

Results

Nine out of ten patients completed the study. One patient in the ointment group received treatment but never returned to the site for follow-up visits. Baseline characteristics are shown in Table 1. Investigator assessments at 24 hrs after treatment revealed improvement by at least one point in all the patients in the CO2 gel mask group compared with the control ointment group, which also showed improvement but to a lesser extent (Figure 1). Evaluation of the skin quality attributes by blinded investigator similarly showed that the CO2 gel and ointment resulted in improvement in all attributes of skin quality one day after treatment, but improvement was greater in the CO2 mask group (Figure1). Results of the blinded investigator assessments were similar at the one-week time point, with the CO2 mask outperforming the ointment in all attributes evaluated. Representative images from a patient in each group are shown in Figures 2 and 3. Subject self-evaluation of their skin quality at 24 hours and one-week post treatment were similar to those of the blinded investigators; more than 1 point change improvement on the 10-point scale was observed in patients in the CO2 gel mask group for all attributes,

compared with a more modest change of half a point in the ointment group (data not shown). At day 7, all (100%) of the patients in the CO2 gel mask group were ''very satisfied'' with the treatment outcomes, while 75% of the control ointment-group patients reported being ''satisfied''.

In regard to the products features (feel on skin, drying time, scent, stickiness, ease of use), patients were extremely satisfied with the CO2 gel masks' cosmetic properties.

Analysis of tolerability assessments by blinded investigator ratings showed great improvement of dryness, scaling, edema, and erythema at the 1 day follow up in the CO2 gel mask group compared to the control group (Figure 4). Erythema was more pronounced immediately after and up to 45 min after treatment in the ointment group compared with the CO2 gel mask group (Figure 2 and 3). Collectively these results showed accelerated recovery and healing in the CO2 gel mask group compared with the control group.

Instances of dryness, scaling and edema in patients of the control group self-resolved within 10 days of treatment.

No unexpected adverse events were reported during the treatment or for the duration of the study in any participant.

Discussion

Since minimally invasive procedures are becoming increasingly popular, offering state-of-art postoperative care to maximize the clinical improvement, safety and minimize downtime has become an area of great importance in the patient and clinical community.

In this pilot clinical study, we present that a CO2 gel mask applied post nanofractional radiofrequency treatment resulted in reduced downtime, speedy healing, improved clinical outcomes, and high patient satisfaction compared with patients that applied a standard of care ointment.

The delivery of carboxytherapy through the CO2 gel mask is an innovative medical application that to our knowledge has not been previously studied or published. While we show herein improvement in aspects of photoaging, and skin rejuvenation, the positive results of our study point to the ability to use this application for other indications, such as relieving irritated skin, accelerating healing of burns, and even potentially acting synergistically with prescription medication to augment the effect they exert in dermatologic conditions such as acne, eczema, or psoriasis. Moreover, while the safety and functional effect of the CO2 gel mask were the focus of the study, its favorable cosmetic properties increase its attractiveness and appeal to be integrated in a post-treatment care regimen.

Specific to our study, the mechanism via which the CO2 gel can reduce downtime and improve skin rejuvenation is hypothesized to be associated with its physical properties (non-occlusive, sterile formulation that can cover surfaces evenly with no irregularities), and also its mechanism of action. With increase of vasodilation, localized influx of growth factors, and chiefly dampening of the inflammatory response post nanofractional radiofrequency, the CO2 gel mask can circumvent the ''injury'' phase of wound healing and step ahead to the repair phase. This translates in speedy recovery as by mediating anti-inflammatory action it can lead to rapid reduction of erythema, stimulation of neocollagenesis, barrier repair, and avoidance of post-inflammatory pigmentation. Indeed, pigmentation was greatly improved within a day and up to seven days in the study. Appearance of wrinkle severity was also decreased, most likely due to increased hydration of the stratum corneum that led to smoother skin surface and elimination of fine lines.

Our study has of course limitations that revolve around the small number of participants in each cohort and the brief follow up time. Future studies will focus on a great sample size

that will allow rigorous statistical analysis of the demonstrated effects and longer followup times. The benefit of the CO2 gel mask after more aggressive procedures such as ablative lasers is also an area that merits evaluation.

Overall, this clinical study provides evidence of the advantageous effect of a novel CO2 gel mask in reducing downtime and enhancing skin rejuvenation after nanofractional radiofrequency, thus introducing an alternative to traditional standard of care postoperative option such as petrolateum-based ointments. A minimally invasive treatment together with an aftercare regimen using the CO2 gel mask that can decrease downtime and enhance neocollagenesis can be considered a next-generation combination protocol for skin rejuvenation and photoaging.

References

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Table 1 Demographic and baseline characteristics of subjects enrolled in the study

Age (years; range)	46 (26-59)
Ethnicity (%) **Hispanic** **Non-Hispanic**	25% Asian 16.7% Non Hispanic Other 16.7% Hispanic Other 41.7% Hispanic, White
Fitzpatrick Skin Type (%)	8.3% FST 2 33.3% FST3 50% FST 4 8.3% FST 5

Table 2: Investigator global asssessments for photodamage, pigmentation, wrinkles and skin quality attributes for the ointment and CO2 gel mask group at baseline, 1 and 7 days after treatment

Time (days)	0	1 days	7 days
IGA photodamage			
Ointment	2.0 (0.2)	1.6 (0.7)	1.8 (0.7)
CO2 gel mask	2.5 (0.9)	1.5 (0.3)	1.7 (0.2)
IGA pigmentation			
Ointment	2.3 (0.3)	2.1 (0.9)	2.1 (0.3)
CO2 gel mask	2.4 (0.3)	1.3 (0.2)	1.5 (0.8)
IGA wrinkles			
Ointment	2.4 (0.3)	2.2 (0.6)	2.0 (0.8)
CO2 gel mask	2.7 (0.2)	1.7 (0.5)	1.7 (0.8)

Figure Legends:

Figure 1: Blinded investigator assessments for IGA and skin quality 1 day post treatment

Figure 2: 27-year old female patient FST 2 before (A), immediately after (B), 45 min after (C) and 1 day after (D) treatment with nanofractional radiofrequency.

Figure 3: 58-year old female patient FST 3 before (A), immediately after (B), 45 min after (C) and 1 day after (D) treatment with nanofractional radiofrequency.

Figure 4: Tolerability assessments in the CO2 mask and ointment group.

Figure 1

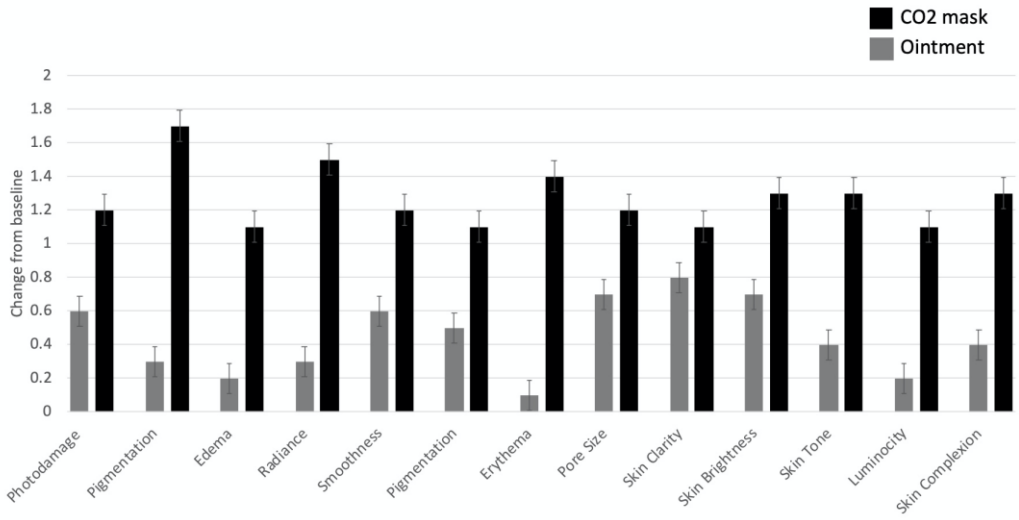
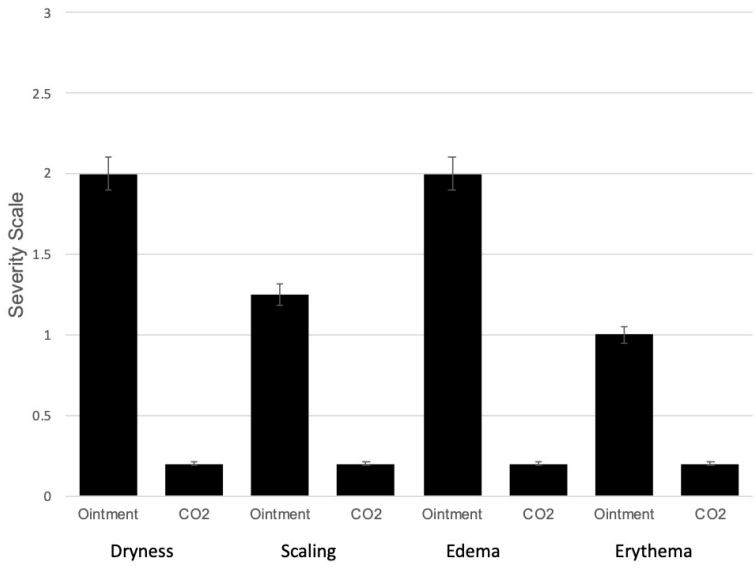

CO2 mask
Ointment
Change from baseline
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Photodamage
Pigmentation
Edema
Radiance
Smoothness
Pigmentation
Erythema
Pore Size
Skin Clarity
Skin Brightness
Skin Tone
Luminocity
Skin Complexion

Figure 2

Figure 3

Figure 4


3
2.5
2
1.5
1
0.5
0
Severity Scale
Ointment
CO2
Ointment
CO2
Ointment
CO2
Ointment
CO2
Dryness
Scaling
Edema
Erythema