EVALUATION OF SAFETY AND EFFICACY OF THE TRIFRACTIONAL RF TECHNOLOGY FOR TREATMENT OF FACIAL WRINKLES

Michael H. Gold M.D¹, Jeffery Adelglass M.D²

¹Tennessee Clinical Research Center Inc., Nashville, TN, USA.

² Texas Pharmaceutical Research, Research Across America, Plano TX, USA.

ABSTRACT

Introduction: Skin resurfacing is an accepted gold standard for the treatment of skin laxity, photodamage and appearance of visible lines and wrinkles. However, the relatively significant risk and the long downtime associated with whole area resurfacing treatments have led to the introduction of fractional resurfacing lasers and radiofrequency (RF) technologies. This study was performed in order to evaluate the safety and efficacy of the new TriFractional technology using the 3F Applicator (A3F), designed to enable skin resurfacing and treatment of wrinkles using fractional RF energy.

Methods

32 Subjects were recruited in two sites and were treated with the A3F for the reduction of facial wrinkles and followed for 3 months after the last treatment. The safety of using the TriFractional system was established by the physicians' assessments and observations of adverse events after each treatment. To evaluate treatment efficacy, subject's pre treatment and post treatment digital images were assessed and graded by two blinded uninvolved physicians based on Fitzpatrick Wrinkle and Elastosis scale.

Results

No significant adverse side effects were detected or reported. Evaluation of photographs of study subjects at baseline and 3 months follow up by the two blinded physicians, revealed improvement (downgrade of at least 1 score according to the Fitzpatrick scale) in 80% and 73% of subjects as graded by the 2 reviewers. Study subjects reported no pain to moderate pain during treatment with no need of pain relief medication beyond topical anesthesia. The majority of study subjects (83.3%) noted that treatment results met their expectations to different extent levels, and most of study subjects (70%) indicated that they will recommend the A3F treatment to their friends.

Conclusions

The results of this study clearly indicate that the TriFractional technology using the 3F applicator provides a safe, tolerable and effective treatment of facial wrinkles.

Key words: radiofrequency, wrinkle reduction, anti-aging, skin resurfacing, TriFractional Running title: Safety and efficacy of TriFractional treatment Correspondence: Michael H. Gold, M.D., Tennessee Clinical Research Center, 2000 Richard Jones Road, Suite 223 Nashville, TN 37215 USA

E-mail: goldskin@goldskincare.com

INTRODUCTION

Skin laxity, photo-damage, appearance of visible lines and wrinkles, and an overall decline in skin texture are typical characteristics of aging human skin¹. An increased demand for aesthetic treatments for enhancing appearance has led to the development and introduction of a myriad of technologies and treatment options. Skin resurfacing has been shown to be highly effective for improving a wide variety of aging skin symptoms, resulting in epidermal renewal and a better organized and newer dermal matrix. Numerous methods are available for skin resurfacing, including chemical peels, dermabrasion, lasers and recently fractional RF².

Continuous wave carbon dioxide (CO2) lasers were first introduced for skin resurfacing in the mid 1980's as an alternative to chemical peels. However, due to many adverse effects associated with this technology, short-pulse, focused-beam CO2 lasers in addition to erbium doped yttrium aluminum garnet lasers (Er:YAG) were introduced, which remove skin in a precisely controlled manner, enabling impressive clinical results for treatment of photo damaged and ageing skin. Unfortunately, full skin laser resurfacing technologies are associated with prolonged healing, significant down time and high complication rates, particularly in darker skin patients, due to the fact that the entire epidermis and papillary dermis are removed, often over large skin areas such as the entire face^{3,4}.

To overcome the complications and risks associated with full skin resurfacing, a new generation of fractional laser resurfacing technologies was introduced in 2003 (Solta Medical, Hayward, CA), opening a window to safer, faster healing skin resurfacing options^{5,6}. Rather than treating an entire skin surface, the fractional laser treats a condensed matrix of small "islets" of tissue leaving intact skin in-between these islets. The unaffected intact "islets" enable an immediate healing process of the treated surface, reducing downtime and risk of complications. Many fractional laser systems have since been introduced and cleared for marketing worldwide, mostly based on CO2 and Erbium YAG laser technology⁷⁻⁹.

Over the past decade Radiofrequency (RF) has become a well-established energy for noninvasive aesthetic treatments of face and body¹⁰⁻¹². In the past several years, fractional RF resurfacing technology has been introduced and has become an accepted method for skin resurfacing.

Similar to fractional laser skin resurfacing, fractional RF systems allow controlled fractional skin resurfacing with minimal downtime in a safe manner. Fractional RF systems affect the epidermal layer, inducing an effective micro-ablative skin resurfacing while simultaneously enhancing the dermal layer. The combined effect results in an improved appearance of wrinkles, fine lines and acne scars¹³. The novel TriFractional approach using the new A3F applicator from Pollogen[®] is designed to enable fractional skin resurfacing for treatment of wrinkles along with skin enhancement via controlled epidermal micro-ablation and concomitant dermal remodeling¹⁴.

The current study was conducted in order to evaluate the efficacy and safety of the TriFractional technology using the A3F for treatment of facial wrinkles. Clinical evidence is provided to demonstrate A3F treatment safety and efficacy.

METHODS

The study was conducted in 2 centers in the USA: Tennessee Clinical Research Center Inc., Nashville, TN, and Research Across America, Plano, TX. The study was approved by Independent IRB, Inc, Plantation, FL.

A total of 32 subjects were recruited to the study after signing an Informed Consent and meeting all inclusion/ exclusion criteria.

Exclusion criteria included pregnancy or breastfeeding, any implanted electronic device, any active dermatological or collagen or vascular disorders, history of skin cancer, prolonged intake of medication that can affect healing, tendency to keloid scaring, any severe concurrent conditions, metal implants in treated area (not including dental implants), and specific aesthetic procedures in the treatment area prior to the study.

Subjects received 3 treatments, spaced 3 weeks apart, with A3F for improvement of wrinkles, and were followed 1 and 3 months after the last treatment.

Prior to each treatment and at each follow up visit, the treatment area was assessed visually and photographed at standardized conditions using high resolution digital photography for producing high quality images, for enabling accurate assessment of wrinkle improvement by blinded evaluators.

Technology

The TriFractional applicator (A3F) is indicated for skin resurfacing and for the treatment of wrinkles by means of micro-ablation and coagulation. A disposable treatment tip, containing a matrix of bi-polar tiny electrodes, is attached to the distal end of the applicator and is placed on the skin for treatment. Radiofrequency current is delivered sequentially between each of the pin electrodes and the large electrodes which surround the pin matrix. Due to this design, a relatively high RF power density is generated in the tissue under each electrode, resulting in fractional treatment micro-wounds in the epidermis which is in direct contact with the electrodes while heat is delivered deeper into the dermis. This fractional manner of energy delivery leaves intact zones in between the directly affected areas which serve as a reservoir of healthy cells to promote a faster, more effective wound healing. The A3F emits a "train" of three sub-pulses with a very short Thermal Relaxation Time (TRT), in one treatment pulse. This modality enables an enhanced effect of deeper penetration and optimized efficacy, with less discomfort to the patient and a deeper gradual thermal effect. Shortly after treatment there is moderate skin erythema and edema in the treated zone, which resolves within 1 - 3 days. During the healing phase, small pin-point

epidermal crusts may appear at each micro-ablated spot which exfoliate naturally after a few days leading to mild epidermal resurfacing.

Visits and Treatments

Prior to treatment, the treated area was cleaned and dried thoroughly and a topical anesthetic agent was applied (Emla, AstraZeneca, Wilmington, DE), according to manufacturer guidelines.

The A3F was placed on the skin with slight pressure to ensure good contact, in areas with uneven skin surface; the treatment area was slightly "stretched" before placing the applicator. During the first treatment of all subjects, the Low parameters program was used. At following treatments, higher parameter programs were used, according to individual skin condition, subject's needs and skin response. Immediately after the treatment, the treated area was visually assessed for skin responses, including edema and erythema and responses were documented. Subjects were instructed to avoid exposure to sun and to apply sunblock daily.

Follow-up visits were intended for assessing the treated area and for acquiring subjects' photographs. At the last (3 months) follow-up visit, subjects were asked to rate level of satisfaction from the cosmetic improvement by filling out a satisfactory questionnaire and the investigators were asked to fill in a general questionnaire evaluating the technology and an individual questionnaire evaluating the improvement of each subject.

Study end points

For treatment efficacy evaluation, baseline and 3 months follow-up photographs of each subject were randomly presented and scored by two independent physicians (blinded evaluators) using the Fitzpatrick Wrinkle and Elastosis scale (Table 1)¹⁵.

Scores of baseline and 3 months follow up photographs were compared.

Success of subject's treatment was defined as a downgrade of at least 1 score according to the Fitzpatrick Scale at 3 months follow-up compared to baseline.

Class	Wrinkling	Score	Degree of Elastosis
Ι	- Fine Wrinkles	1-3	<i>Mild</i> (fine textural changes with subtly accentuated skin lines)
II	- Fine to moderate depth wrinkles	4-6	<i>Moderate</i> (distinct papular elastosis [individual papules with yellow translucency
	- Moderate number of lines		under direct lighting] and dyschromia)

III	- Fine to deep wrinkles	7-9	Severe
	- Numerous lines		(multipapular and confluent elastosis
			[thickened yellow and pallid]
	- With or without redundant		approaching or consistent with cutis
	skin folds		rhomboidalis)

Table 1: Fitzpatrick wrinkle classification system

Safety of the procedure was determined by monitoring any occurrence of adverse effects or complications directly related to the treatment, during or after the treatment.

Subject satisfaction was gathered from subject's questionnaires completed at 3 months follow-up.

Investigators' satisfaction from treatment results of each subject was gathered from the investigator questionnaires.

RESULTS

32 healthy subjects were recruited to the study (30 females and 2 males), ages 40-64 (Mean age 51.22 ± 7.31 years) and Fitzpatrick skin type 2-5. Of the 32 subjects recruited, 30 subjects who completed the full study course and were followed to the 3 months follow-up were included in efficacy evaluation. One subject withdrew consent after 2 treatments due to work schedule; an additional subject was lost to follow-up. 1 subject of the 30 subjects that completed the study course and included in efficacy evaluation underwent only 2 A3F treatments due to personal constraints. For assessing safety of the A3F, results of all 32 subjects that were treated were used.

Treatment Safety

The data of all 32 subjects who underwent treatment were analyzed. As expected, mild to moderate erythema and several cases of mild edema (5 cases, 16%) were detected at the site of treatment, all cases resolved without treatment, within a few hours. In most cases, scabs appeared within several days (average 2.53 ± 1.15) and lasted several days (average 5.63 ± 2.3). Three mild related adverse effects were reported during the study (hyper pigmentation; redness and acne break out), all 3 cases resolved spontaneously within 1-2 months. There were no incidences of infections, scarring, hypopigmentation or any other serious complications. Treatments were well tolerated with minimal to no pain by the majority of study subjects (75%; 62% and 58% of study subjects, at the first, second and third treatment respectively). None of the subjects needed any additional analgesic or other pain medication during treatment.

Treatment Efficacy

Treatment efficacy was determined by objective evaluation of photographs taken at baseline (prior to treatment initiation) and at the 3 months follow-up, by two blinded physicians who arbitrarily (non-chronologically) scored the photos using the Fitzpatrick

Elastosis Scale. The results of 30 subjects that completed the study course were included in the efficacy analysis.

Analysis revealed an improvement in wrinkle appearance in the majority of study subjects (80% according to one reviewer and 73.3% according to the second reviewer). Score differences were found to be statistically significant (p<0.001) for both reviewers, further indicating treatment efficacy. Table 2 and Figure 1 represent averages (\pm STDV) of Fitzpatrick scores given by the two reviewers at baseline and 3 months follow-up.

In order to evaluate level of agreement between the two uninvolved physicians, statistical comparison (using two sided paired TTest) was conducted between the baseline wrinkle and elastosis score provided by the two blinded reviewers. The statistical analysis failed to reveal significant differences (p > 0.05) between the baseline wrinkle score of the two reviewers. Furthermore, same result was obtained while comparing the 3 months follow-up scores of the two reviewers. The statistical comparison of the 3 months follow-up wrinkle and elastosis score, obtained by the two uninvolved evaluators, indicates no statistical difference (p > 0.05) between the two reviewers. These results indicate that both uninvolved reviewers were in agreement regarding wrinkle and elastosis degree, at baseline as well as at 3 months follow-up, enhancing the study results. Table 2 summarizes the uninvolved physicians score at baseline and 3 months follow-up.

Average Wrinkle and Elastosis Score									
		1 st Reviewer			2 nd Reviewer				
Score time	Average Score	Score reduction (compared to baseline)	Statistical (TTest) Results of the Comparison	Average Score	Score reduction (compared to baseline)	Statistical (TTest) Results of the Comparison			
Baseline	4.47 (±1.43)		-	4.10(±1.24)	-	-			
3 months follow-up	3.43(±1.33)	1.03(±0.76)	p<0.001	3.20(±1.24)	0.90(±0.55)	p<0.001			

Table 2: Averages (± STDV) of wrinkle and elastosis scores given by the two uninvolved reviewers at baseline and 3 months follow-up (after treatments), score reduction comparing to baseline, and statistical results of the comparison.





The following sets of before and after photographs (Figures 2-5) illustrate the significant beneficial effect achieved by the TriFractional treatments.



Figure 2: A 49 year old female. **A** – Baseline, **B** - 3 months follow-up Figure **B** portrays tighter firmer looking skin and a reduction in fine wrinkles.



Figure 3: A 56 year old female. A – Baseline, B – at 3 months follow-up Figure B - Skin complexion is brighter and a general improvement in facial contouring is noticed following skin tightening. Notice peri-orbital fine wrinkle and a naso-labial fold reduction



Figure 4: A 64 year old female.A – Baseline,B - 3 months follow-upFigure B clearly portrays a fresher, more even skin surface, with corrections to scarring and skin tone imperfections in a subject with skin type V.



Figure 5: A 46 year old female. A. Before A3F B. 1 month after 3 A3F treatments

A brightening and evening out of skin tone are noticed in figure **B** where epidermal renewal enables for enhanced skin appearance 1 month after A3F treatments.

In addition to the efficacy evaluation by the two blinded evaluators, efficacy was further demonstrated when reviewing the Fitzpatrick wrinkle and elastosis scores of the subjects as graded by each PI following a visual observation of subject's skin at baseline and at 3 months follow up visit. The average wrinkle and elastosis score given by the PIs at baseline was $4.84(\pm 1.05)$ and at 3 months follow up was 3.43 (± 0.97), a reduction of 1.41 (± 0.96) in average score.

At the 3 months follow-up visit subjects were asked to rate level of satisfaction from the treatments. Vast majority of study subjects (25 - 83.3%) noted that treatment results met their expectations to various extents, majority of study subjects (25 subjects - 83.3%) noticed an improvement of skin texture. Vast majority of study subjects (21 subjects - 70%) noted that they would recommend the TriFractional treatment to friends. These results indicate that most of study subjects found the TriFractional treatment effective and tolerable.

DISCUSSION AND CONCLUSION

Skin resurfacing and treatments of wrinkles have evolved rapidly over the past 15 years from ablative to minimally ablative methods and recently to fractional resurfacing.

RF skin resurfacing is an effective method for facial enhancement as the epidermis is renewed over a short time allowing for a more uniform skin tone. In the dermis, the

thermal effect following epidermal ablation results in enhanced skin tightening through rebundling of existing collagen and through generation of new collagen via process of neocollagenesis that will continue several months past the procedure¹⁶.

Hruza et al. evaluated the effect of a fractional RF applicator (MatrixTM RF by Syneron, Israel) for skin rejuvenation and wrinkle reduction¹⁷. According to the authors, subjects undergoing facial treatments experienced minimal pain, no permanent side effects, nor significant downtime. They concluded that fractional RF skin resurfacing results in a safe, tolerable and effective treatment for improvement of skin brightness, tightening, texture and for reduction of fine wrinkles. The depth of tissue ablation, coagulation and necrosis were found to be controllable and correlated to treatment power and coverage and could be modulated to optimize treatment of variable dermatologic conditions.

In a previous publication on the A3F, clinical effects post treatment demonstrated reduction of fine wrinkles, improved appearance of acne scars, a general improvement of skin texture and scar tissue, skin brightening, skin tightening, improvement of skin irregularities and reduction in pore size¹⁴. Histological results following ex vivo and in vivo treatments confirmed the pattern of fractional effect by zones of epidermal ablation with dermal collagen condensation below accompanied with skip zones of unaffected tissue. The controlled fractional effect resulted in epidermal renewal and dermal collagen remodeling and regeneration.

In the clinical study reported in this document, treatment results demonstrated the safety and effectiveness of the fractional A3F for skin resurfacing allowing treatment of fine facial wrinkles, enhancing facial contour through skin tightening and improving complexion through epidermal renewal. As mentioned, the immediate effect post treatment was mostly erythema and edema followed by tiny scabs that subsided after a few days. Erythema and edema are a normal response of the inflammatory process induced following the micro wounds created by the treatment and are an indication of an effective wound healing process¹⁸. The micro wound healing results in a renewal of the epidermal layer and neocollagenisis in the dermis, a process that continues several weeks after the treatment. The fractional manner of treatment with healthy intact zones allows for faster healing with no down time or discomfort to the subjects. The Principle Investigators completed an IRB approved questionnaire addressing their satisfaction from treatment effects, assessed skin texture improvement in 97% of the subjects (29 out of 30 subjects). A certain level of wrinkle improvement as a treatment outcome was mentioned for 90% of the subjects (27 out of 30 subjects).

As demonstrated in Figure 4, the A3F treatment was found to be safe and effective for dark skin types resulting in improved skin complexion, evening out of skin tone and imperfections. This result indicates a major advantage of the TriFractional technology over other existing resurfacing options.

One case of post treatment acne was reported in this study. Acne break outs have been

reported as an expected side effect for patients with a history of acne following CO_2 fractional resurfacing¹⁹.

This specific study was for evaluation of the A3F for treatment of wrinkles; no objective measurable data was gathered to evaluate and grade skin tone improvement, texture improvement or general skin tightening. However, review of subjects' photos and subject's feedback of improved skin texture, definitely demonstrate the effect of skin resurfacing and the evening out of skin tone imperfections, most pronounced at 1 month post treatments, as the epidermal layer is freshly renewed and rejuvenated. (Figure 5)

This study clearly demonstrates that the TriFractional technology using the A3F is a safe and effective method for skin resurfacing resulting in a reduction of wrinkles and enhanced skin and facial appearance.

Acknowledgement: This study was funded by Pollogen Ltd.

REFERENCES

- 1. Fisher GJ, Varani J, Voorhees JJ. Looking older: Fibroblast collapse and therapeutic implications. Arch Dermatol. 2008; 144:666-672.
- 2. Alexiades-Armenakas MR, Dover JS, Arndt KA. The spectrum of laser skin resurfacing: nonablative fractional and ablative laser resurfacing. J Am Acad Dermato. 2007; 58:719-737.
- Nanni CA, Alster TS, Complications of CO2 laser resurfacing: an evaluation of 500 patients. DermatolSurg. 1998;24:315–320.
- Tanzi EL, Alster TS. Side effects and complications of variable pulsed erbium: YAG laser skin resurfacing: extended experience with 50 patients. Plast Reconstr Surgery, Vol.111, No.4, 2003, pp.1524–1529.
- Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers in Surgery and Medicine, Vol.3, No.4, 2004, pp.426–438.
- Laubach HZ, Tannous Z, Anderson RR, Manstein D. Skin responses to fractional photothermolysis. Lasers in Surgery and Medicine. Vol.38, No.2, 2006, pp.142–149.
- Tierney EP, Eisen RF, Hanke CW. Fractional CO2 laser skin rejuvenation. Dermatologic Therapy, Vol. 24, 2011, 41–53A.
- Chapas AM, Brightman L, Sukal S, Hale E, Daniel D, Bernstein LJ, Geronemus RG. Successful Treatment of Acneiform Scarring With CO2 Ablative Fractional Resurfacing. Lasers in Surgery and Medicine 40:381–386 (2008)
- Trelles MA, Ve' lez M, Mordon S. Correlation of Histological Findings of Single Session Er:YAG Skin Fractional Resurfacing With Various Passes and Energies and the Possible Clinical Implications. Lasers in Surgery and Medicine 40:174–177 (2008)
- Boisnic S, Branchet C. Ex Vivo human skin evaluation of localized fat reduction and anti aging effect by TriPollar radio frequency treatments. Journal of Cosmetic and Laser Therapy. 2009 early online 1-7
- 11. Levenberg A. Clinical experience with TriPollar radiofrequency system for facial and body aesthetic treatments. Eur J Dermatol 2010; 20 (5): 1-5
- 12. Gold MH. Tissue tightening: a hot topic utilizing deep dermal heating. Journal of Drugs in Dermatology. Dec-2007, Vol 6 Issue 12, 1238-1242
- Hantash BM, Ubeid AA, Chang H, Kafi R, Renton B. Bipolar Fractional Radiofrequency Treatment induces Neoelastogenesis and Neocollagenesis. Lasers in Surgery and Medicine 41:1–9 (2009)
- Levenberg A, Gat A, Boisnic S, Branchet MC. Treatment of Wrinkles and Acne Scars Using the TriFractional, A Novel Fractional Radiofrequency Technology - Clinical and Histological Results. Journal of Cosmetics, Dermatological Sciences and Applications, 2012, Published Online September 2012 (http://www.SciRP.org/journal/jcdsa)

- 15. Fitzpatrick RE, Goldman MP, Satur NM, Tope WD. Pulsed carbon dioxide laser resurfacing of photo-aged facial skin. Arch Dermatol. 1996; 132:395-402.
- Orringer JS, Kang S, Johnson TM, Karimipour DJ, Hamilton T, Hammerberg G, Voorhees JJ, Fisher GJ. Arch Dermatol.2004 Nov. VOL 140: 1326-1332
- Hruza G, Taub AF, Collier SL, Mulholland SR. Skin Rejuvenation and Wrinkle Reduction Using a Fractional Radiofrequency System. Journal of Drugs in Dermatology. 2009; 8: 259-265.
- Martin P. Wound Healing—Aiming for Perfect Skin Regeneration. Science, 1997 April, Vol 276: 75-86
- 19. Alster TA, Tanzi EL, Lazarus M. The Use of Fractional Laser Photothermolysis for the Treatment of Atrophic Scars. Dermatologic Surgery 2007;33:295–299