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CLINICAL REPORTS

Treatment of periorbital wrinkles using thermo-mechanical fractional injury therapy versus fractional non-ablative 1565 nm laser: A comparative prospective, randomized, double-arm, controlled study

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Abstract

Background: Non-ablative fractional laser is an effective modality for the treatment of periorbital wrinkling, one of the earliest signs of skin aging. Thermo-mechanical fractional injury (TMFI) therapy (Tixel®, Novoxel®, Israel) is an innovative technology that is now being used for facial skin rejuvenation. Our study compares the clinical results, side effects, and downtime profile between TMFI treatment and non-ablative fractional 1565 nm laser (ResurFX®, Luminis, Israel).

METHODS: This was a prospective study of 68 patients (64 women, 4 men) with skin types I–VI in two medical centers (34 from Israel, 34 from the USA) that were randomized to receive either TMFI or NAFL treatment for periorbital wrinkling. Patients received 3–5 treatments, 3–5 weeks apart. Six months after the last treatment, the change in Fitzpatrick Wrinkling Classification System (FWCS) was calculated by three non-involved physicians and compared to pretreatment results. Side effects and downtime profiles were assessed in each group (including VAS pain assessment, time required to refrain from work and social activity, and time required for the resolution of redness, edema, and crusts.)

RESULTS: A moderate improvement in periorbital wrinkling was demonstrated in both groups, with an average improvement of 1.6 ± 0.6 in FWCS in the TMFI group and an average improvement of 1.7 ± 0.8 in the NAFL group ($p < 0.001$). Postprocedural VAS score was 5.86 ± 2.3 in the NAFL group and 4.01 ± 2.6 in the Tixel® group. Approximately 80% of subjects returned to both work and social activities two days postprocedure. Crusts were reported by 52% of patients in the TMFI group, compared to 16% of patients in the NAFL group more than 48 hours postprocedure ($p < 0.05$). There were no statistically significant differences in the other parameters between the two groups.

CONCLUSION: TMFI is an effective and safe modality for the treatment of periorbital wrinkling, with comparable results to the 1565 nm NAFL.

KEYWORDS
non-ablative fractional laser, periorbital rejuvenation, periorbital rhytides, periorbital wrinkling, thermomechanical fractional injury

INTRODUCTION

The periorbital area is one of the most challenging aesthetic regions to treat,[1] as most patients present with multiple changes, including edema, fine and coarse wrinkles, hyperpigmentation, dryness, and uneven texture.[2] Several modalities improve periorbital wrinkling. Aggressive invasive procedures are more likely to yield improved cosmesis but can result in longer downtime and a higher rate of adverse effects.[3–8] Non-ablative fractional 1565 nm Er:glass fiber laser (NAFL), was recently demonstrated to offer a mild-moderate improvement in periorbital wrinkling,[9] and was cleared for marketing this indication by the US Food and Drug Administration (FDA).

The Tixel is a non-laser, non-radiofrequency, thermomechanical fractional skin treatment device intended for cutaneous procedures requiring coagulation of soft tissue; it transfers heat to the skin directly without emitted radiation. Thermal energy is delivered to the tissue via a tip consisting of a grid of miniscule titanium pyramids. The tip is heated within the handpiece, and it is rapidly projected forward to contact the skin surface and coagulate tissue, creating microcraters of minor damage by evaporation and desiccation. The amount of thermal energy delivered to the skin is determined by the pulse duration (PD; range: 5–18 milliseconds) and protrusion distance or depth (100–1000 µm). The protrusion is defined as the distance the tip projects from the edge of the handpiece. A greater protrusion distance leads to a greater degree of skin contact between the titanium pyramids, thus fewer air gaps and greater thermal transfer are achieved. Importantly, thermal transfer in thermomechanical fractional injury (TMFI) spares the epidermis from full penetration. Representative histology of the skin damage from the Tixel in prior studies[10] are enclosed demonstrated in Figure 1.

Safety goggles are not required. Such technology offers an user-friendly method for performing fractional skin treatment, including the periorbital region and was recently demonstrated to moderately improve periorbital wrinkling as well.[11]

The purpose of this clinical trial is to compare the efficacy and adverse event (AE) profile of TMFI with 1565 nm Er:glass fiber laser in the treatment of periorbital wrinkling.

METHODS

This was a prospective, double-arm, randomized study of 68 patients with mild to moderate periorbital wrinkles, in two centers (Tel Aviv, Israel, and New York, NY, USA)

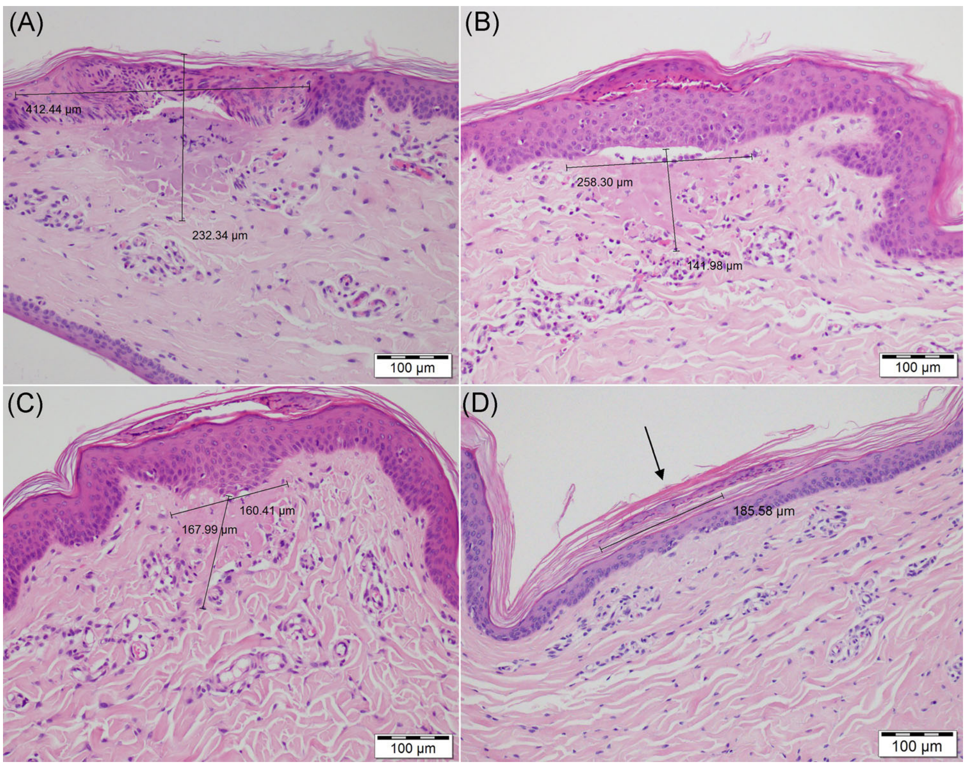

FIGURE 1 Representative skin biopsies in pigs demonstrate the following: (A) Immediately post Tixel treatment, a wedge-shaped dermal area of collagen coagulation (acute thermal necrosis), with no immediate (acute) inflammation, edema, or hemorrhage is found with capillary dilation. (B) At 24 hours posttreatment, thermal necrosis remains in both the dermis and epidermis. There may be separation of the dermoepidermal junction with minimal numbers of leukocytes and a serocellular crust with viable epidermis. (C) After 3 days, the epidermis is regenerated and remnants of degenerated dermal collagen are observed with separation of the dermoepidermal junction as well as scant number of leukocytes are observed. (D) At 14 days, there is a complete regeneration of lesions with minimal crust and minimal superficial fibroblast proliferation

using TMFI (34 patients) or NAFL (34 patients) that was conducted between March 2018 to November 2019. Three to five monthly treatments were performed, and patients were assessed during follow-up visits at 1, 3, and 6 months after the final treatment. The study was approved by an ethics committee/institutional review board and was performed consistent with the ethical standards of the Declaration of Helsinki. The participation in the study was voluntary, and participants were allowed to withdraw from the study at any time. Informed consent was obtained from each subject.

Participants

Inclusion criteria were as follows: healthy males or females, Fitzpatrick skin types I–VI, aged 40–70 years with clinically evident periorbital wrinkling who were willing and able to provide informed consent. Exclusion criteria were as follows: women who are pregnant or lactating; severe sun damage, keloid scarring or open wounds in the treatment areas; a prior cosmetic procedure to improve facial rhytids (i.e., rhytidectomy, periorbital or eyelid/eyebrow surgery, brow lift, CO_2/Erbium/similar laser/fractional resurfacing, or radiofrequency treatment) within 12 months; prior facial treatments with laser, surgical, chemical or light-based facial treatments within the previous 6 months (e.g., botulinum toxin injections, retinoid or glycolic acid treatment, or microdermabrasion); injectable filler in the treatment area within 9 months of the study, permanent facial implant, and inability to understand the treatment protocol or to give informed consent.

Device

The Tixel® (Novoxel®, Israel) is a non-laser, fractional, non-ablative, thermomechanical skin rejuvenation system which combines thermal energy with motion. The thermal energy is delivered to the tissue via a tip. The system consists of two types of tips, (1) a standard tip consisting of 81 (9×9) tiny titanium pyramids, and (2) a small tip (also known as the periorbital tip) consisting of 24 (6×4) tiny pyramids. The tip base is heated to 400°C within a handpiece, which quickly moves towards the skin surface to achieve contact and coagulate tissue, creating microcraters by evaporation and desiccation. The amount of thermal energy delivered to the skin is determined by the pulse duration (PD; range: 5–18 milliseconds) and distance by which the tip apexes extend beyond the distance gauge surface (protrusion) (100–1000 μm). A greater protrusion leads to a greater degree of skin contact between the titanium pyramids, fewer air gaps, and greater thermal transfer. Importantly, thermal transfer in TMFI technology does not involve any mechanical penetration of the epidermis. The fractional thermal effect typically consists of superficial epidermal ablation and vaporization and coagulation of the papillary dermis.

Treatment with both modalities was performed following the application of a topical anesthetic cream. Patients in the TMFI group were treated with both tip types. During each session, subjects received treatment with a constant PD of 10 milliseconds and a constant protrusion depth of 500 μm in one pass. Patients in the NAFL group were treated with the ResurFX™ (Lumenis) using the following settings: treatment density range between 150 and 300/cm^2, scan size: 8–17 mm, (mean 12 mm), and the energy range was 13–25 mJ (mean: 21 mJ).

AEs (redness, edema, and crusting) and downtime (number of days before returning to work and social activities) were recorded after each treatment. Standardized photographs were obtained under the same lighting conditions before each treatment and at the 6 months follow-up visit. The Visia skin analysis system (Canfield) was used in Israel and the Intellistudio system (Canfield) was used in the NY site.

Blinded grading of photographs

The degree of improvement observed following TMFI and NAFL treatments was assessed by presenting pre-treatment and 6-month follow photographs in a randomized order to three independent physicians who were not involved in the study. Scores were assessed using the Fitzpatrick Wrinkle Classification System (FWCS), a scoring system on a scale of 0 (no wrinkles) to 9 (deep and numerous wrinkles). The mean improvement was calculated and compared between the two groups.

Patient questionnaires

Patients evaluated their treatment pain, AEs, and recovery time at each follow-up visit. This consisted of rating the tolerability of the treatment using the Visual Analog Scale (VAS) for pain assessment (1–10), reporting the presence of redness, edema, and crusts (less or more than 2 days post-procedure), and calculating the time to return to work and social activity (less or more than 2 days postprocedure). The results were compared between the two treatment groups.

Analyses were mainly descriptive in nature, summarized by count and percentage for categorical variables and mean, median, minimum, and maximum percentiles with standard error for continuous variables. Baseline and posttreatment outcomes were analyzed using Fisher's test for categorical variables. All statistical analyses were performed by SPSS version 25.0 (IBM Corporation).

RESULTS

Sixty-eight patients (34 from Israel, 34 from the United States; 64 women, 4 men) were included in this study. The age of the participants ranged from 40 to 70 years

TABLE 1 Demographics and treatment characteristics

Demographics	Tixel N	Tixel %	ResurFX N	ResurFX %
Gender				
Male	0	0	4	11.8
Female	34	100	30	80.2
Ethnicity				
Asian	2	5.9	2	5.9
Black or African American	0	0	3	8.8
White	30	88.2	24	70.6
Other	2	5.9	5	14.7
Fitzpatrick Skin Type				
I	1	2.9	0	0
II	15	44.1	15	44.1
III	12	35.3	10	29.4
IV	5	14.7	5	14.7
V	1	2.9	2	5.9
VI	0	0	2	5.9
No. of Tx				
3	11	44	9	41
5	13	56	13	59

(average 52 years). Patient's demographics are elaborated in Table 1. Forty-four percent (11 patients) and 41% (9 patients) completed three treatments, while 56% (14 patients) and 59% (13 patients) completed five treatments with TMFI and NAFL, respectively.

Blinded photographic analysis using the FWCS demonstrated a moderate improvement with both devices six months after treatment; there was an average improvement of 1.6 ± 0.6 in the TMFI group (Figures 2 and 3) and an average improvement of 1.7 ± 0.8 in the NAFL group. There was no difference between the two treatment groups with regard to FWCS score improvement ($p > 0.05$), and improvement from baseline was statistically significant for both treatment modalities ($p < 0.001$).

There was a statistically significant ($p < 0.05$) difference in the average pain score using the VAS between the two treatment groups, with a VAS score of 5.86 ± 2.3 in the NAFL group versus $4.01 + 2.6$ in the TMFI group. There was no difference between the two groups in the time required for resolution of erythema and edema. Figure 4 demonstrates the 5-day healing process for a representative patient treated with the Tixel. However, in the TMFI group, crusts lasted for more than 2 days postprocedure and were present in 52% of patients compared to 16% of the NAFL group. There was no statistically significant difference in downtime between the two groups, and 83%/81% of patients returned to work and 79%/77% returned to social activities two days postprocedure for TMFI/NAFL respectively (Figure 5). For most patients, the pinpoint scabbing and crusting that results immediately after treatment can be masked by makeup and lasts from a few hours to 1 day postprocedure. Patients described a mild burning and stinging sensation for 1–2 hours postprocedure.

Three separate subjects (4.4%) reported four total AEs. Two subjects (5.9%) in the TMFI arm reported dry and/or watery eyes, and one subject (2.9%) in the NAFL arm developed uveitis, which was determined to be unrelated to the treatment. All AEs resolved except for the uveitis, the outcome of which was unknown because the patient was lost to follow-up.

DISCUSSION

Periorbital wrinkles are an early manifestation of photoaging. The cause of periorbital wrinkling is multifactorial and includes intrinsic aging, extrinsic aging (largely ultraviolet light exposure), repetitive use of facial muscles with expressions, skin type, hormonal status, genetic inclination, ethnicity, nutrition, and other medical disorders.[12] Periorbital wrinkles may occur as early as the third decade of life and often distressing to patients, causing them to seek rejuvenation procedures.

There are a variety of treatment options to mitigate the signs of periorbital skin aging, including topical retinoids,[13] radiofrequency,[14,15] broadband infrared,[16] intense pulsed light,[17] chemical peels,[18] botulinum toxin,[19] and platelet-rich plasma (PRP),[5] and non-ablative and ablative laser resurfacing procedures.[15,20] Full surface and fractional ablative resurfacing procedures are effective in improving periorbital wrinkles and laxity, but, because the epidermis is ablated, the recovery may take 1–2 weeks, and posttreatment erythema and hyperpigmentation commonly emerge, especially in darker skin types. Fractional ablative resurfacing has safely improved rhytid and periorbital line clearance, but because of the removal of the epidermis, patients treated with CO_2 resurfacing can have many side effects.[21] Over the course of the last decade, NAFL treatments have gained increasing popularity because of the limited recovery time and incidence of AEs, by delivering energy into the dermis without destroying the overlying epidermis.[22] Several studies have corroborated their efficacy in improving skin elasticity and enhanced tightening with minimal AEs and downtime.[9,23,24]

The present study compares the safety and efficacy of two non-ablative fractional technologies in the treatment of periorbital wrinkles: TMFI technology and NAFL with a 1565 nm laser. Blinded evaluation of pretreatment and posttreatment photographs using the FWCS demonstrated similar wrinkle improvement with both

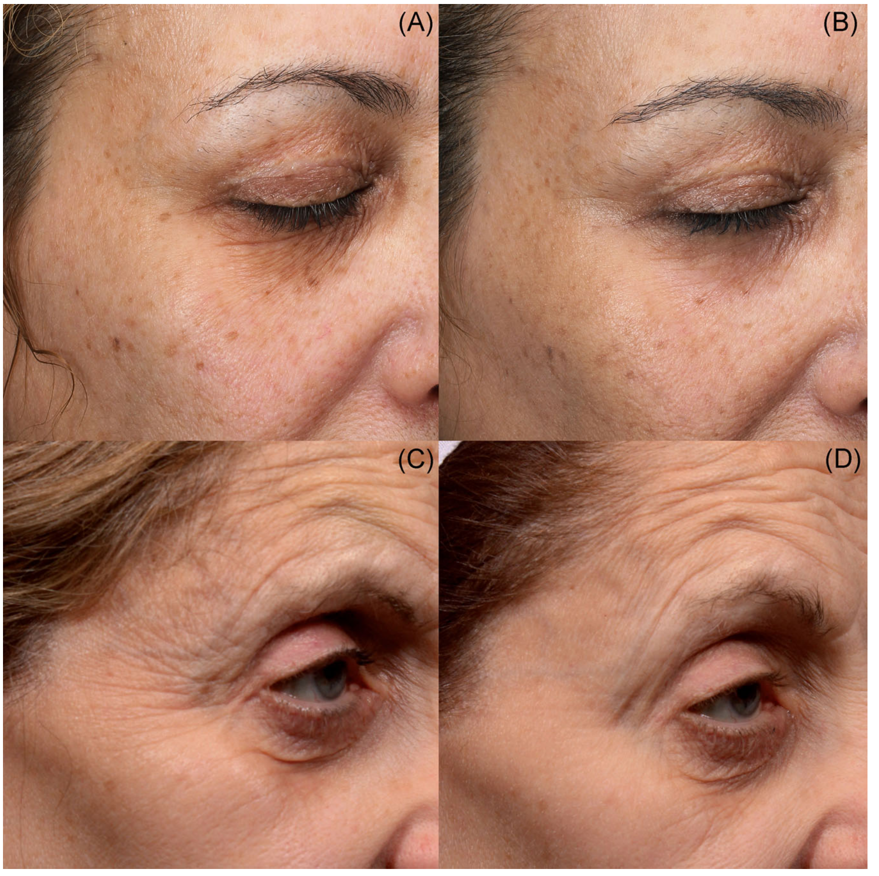

FIGURE 2 Representative patients before (A, C) and after (B, D) 4 (upper) and 3 (lower) Tixel® treatments. Please note the change in periorbital wrinkles

FIGURE 3 Representative patients before (A, C) and after (B, D) 4 (upper) and 3 (lower) Tixel® treatments. Please note the change in periorbital wrinkles

devices. Mean improvement of the FWCS was 1.6 ± 0.6 for TMFI and 1.7 ± 0.8 for the laser. The observed AEs of both devices were mild and transient.

The settings chosen with the NAFL in this study are frequently used and recommended for treatment of periorbital regions. The developers of the Tixel provided recommended settings for periorbital rejuvenation for their device, which was a pulse duration of 12 milliseconds and 600 μm protrusion. In this study, we chose a more conservative approach with a pulse duration of 10 milliseconds and 500 μm protrusion. It has been previously shown that pulse durations around 6 milliseconds are used for drug delivery and those greater than 10 milliseconds are used for rejuvenation; common settings for rejuvenation are 12–14 milliseconds.[11,25,26] As the periorbital region is a sensitive area, coordinating treatment at two centers in different countries with diverse populations warranted more conservative treatment parameters. The depth was chosen based

FIGURE 4 Images of a representative patient's periorbital treatment with the Tixel and recovery at baseline (A, B), Day 1 (C, D), Day 2 (E, F), Day 3 (G, H), and Day 5 (I, J) after treatment

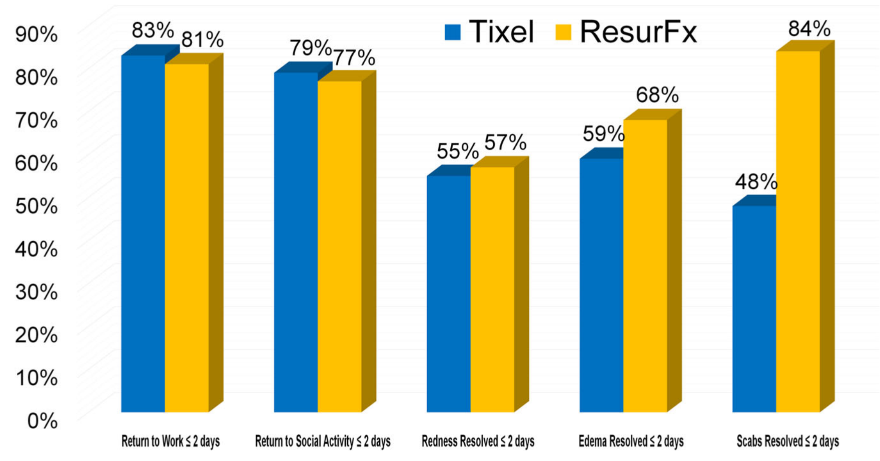

FIGURE 5 A comparison of downtime parameters between the two treatment groups

on the depth of the periorbital skin to the reach the papillary dermis ~300 μm (Figure 1).

The drop-out rate in this study was relatively high, potentially due to poor patient selection and the relatively high number of visits required. However, a lower rate of study withdrawal was observed in the TMFI arm (Tixel: 9/34 [26.5%] vs. laser: 12/34 [35.3%]). This may indicate better patient satisfaction and or lower treatment discomfort and posttreatment pain following TMFI treatment compared with the laser device. The VAS score for pain with the Tixel was significantly lower than with the laser. No statistically significant differences were found between the devices with regard to downtime, with the exception of longer duration of crusts after TMFI treatment. This is an anticipated finding, due to focal epidermal ablation induced by the pyramid tips.

This study has many limitations. Frequently, patients presented with periorbital comorbidities including hypertrophy of the orbicularis oculi muscle, fat herniation, dyspigmentation, and edema, which were not exclusion criteria. Furthermore, this study is limited due to its inability to address the underlying issue of limiting the movement of the orbicularis oculi muscle to mitigate periorbital rhytid formation. It is possible that more pronounced improvement would have been observed if patients with no comorbidities and pure periorbital skin laxity were selected. In this study, a single TMFI pass was applied, yielding 7%–8% active area. To potentially enhance improvement with this therapy in the future, multiple passes should be performed to increase coverage and yield better results.

The patient cohort was limited in size, especially since patients were lost to follow-up, and comparison was performed between treatment arms rather than a split-face design, making it more difficult to control for different posttreatment responses among different patients. As this study was conducted at two separate treatment centers, consistent photography was difficult to maintain. To accommodate our patients, treatment schedules were flexible, allowing for 3–5 treatments, adding an element of inconsistency.

In this study, we demonstrate that the TMFI device is effective in improving periorbital wrinkles with minimal AEs, and recovery time. TMFI technology is an excellent modality for drug delivery owing to its formation of micron-sized wells in the epidermis lined by a thin rim of coagulation.[11,27–29] As wrinkling in the periorbital region is exacerbated by constant contraction of the orbicularis oculi muscles with facial expression, the use of TMFI technology to deliver botulinum toxin may achieve a more profound improvement, by both diminishing muscle contraction and stimulating collagen production and remodeling in a region where the skin is thinnest.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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