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ORIGINAL ARTICLE

Efficacy and safety of a thermal fractional skin rejuvenation system (Tixel) for the treatment of facial and/or scalp actinic keratoses

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Abstract

Actinic keratoses are common cutaneous lesions with a potential to progress to invasive squamous cell carcinoma. Therefore, treatment is crucial. The Tixel® is a noninvasive thermomechanical device designed to transfer heat to the upper dermis in a controlled manner according to a predetermined setting. This study aimed to evaluate the safety and efficacy of a thermomechanical fractional skin resurfacing technology for the treatment of facial and scalp actinic keratoses. A prospective, open-label, before–after study was conducted in a tertiary medical centre from May 2020 to April 2021. Patients presenting with facial/scalp actinic keratoses of mild-to-moderate thickness underwent 2 or 3 Tixel treatments (depending on clinical improvement), 3–4 weeks apart. The reduction in lesion count and overall improvement in appearance were assessed by clinical examination and digital photography. Findings were compared between baseline and follow-up at 3 months after the last treatment session. Patient satisfaction was evaluated by questionnaire, and adverse effects were documented. A total of 20 patients participated in the study. All completed 2–3 treatments and follow-up visits. Assessment of digital photographs was performed by 2 assessors blinded to the timepoint at which each photo was taken (before or after treatment). The average number of lesions at baseline was 9.8 (±4.8) and the mean reduction in lesion count was 7.9 (±4.4) (80.6%). Complete clearance was observed in 31.6% of patients. No adverse effects were noted during treatment and follow-up. Most patients reported being "very satisfied" or "satisfied" with the treatment results (85%) and experience (95%). Treating facial and scalp actinic keratoses with the Tixel device was found to be effective and safe.

Keywords Tixel · Actinic keratosis · Solar keratosis

Introduction

Actinic keratoses (AKs) are common epidermal lesions formed by proliferation of keratinocytes. AKs accounted for an estimated 5.2 million annual healthcare visits from 2000 to 2003 in the USA alone; 62% of the patients were aged 65 years or more [1]. Major risk factors for the development of multiple lesions (10 or more) were male gender, older age, and lighter skin phototype with a high tendency for sunburn [2]. The reported rates of malignant transformation of a single actinic keratosis vary among studies from 0.1 to 16% [3, 4]. The estimated 10-year incidence rate of AK progression to squamous cell sarcoma without proper treatment is about 10%, emphasizing the importance of prevention, follow-up, and treatment [5].

Therapy can be aimed at a solitary lesion (lesion-targeted therapy) using mostly destructive regimens, or field-directed, to reduce clinical and subclinical lesions across an entire

Key message A thermomechanical fractional device (Tixel) is safe and effective in treating facial/scalp actinic keratoses.

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potentially cancerous area [5, 6]. Treatment is individually tailored with consideration of clinical parameters (site and number of lesions), patient characteristics (age, immune system status, and compliance), and treatment cost and tolerability [5, 7]. Lesion-targeted treatment modalities include cryotherapy [8], laser therapy [9], surgical removal (wide or shave excision), and curettage [10]. Field-directed treatment modalities include 5-fluorouracil [11], diclofenac 3% gel [12], chemical peels [13], imiquimod [14, 15], and photodynamic therapy [16, 17]. Oral nicotinamide was found to have various photoprotective effects, and its administration to high-risk individuals led to a reduction in AK and nonmelanoma skin cancer incidence [18].

In recent years, there have been reports on the application of energy-based devices such as lasers for the treatment of nonmelanoma skin cancers [19]. However, their use was limited by high cost, need for technical acumen, and substantial side effects [20, 21].

Tixel® is a thermomechanical system designed to fulfill the clinical need for safe and efficient fractional skin resurfacing. It has been shown to improve skin complexion and attenuate wrinkles. The device consists of a metal element, termed the tip, made up of an array of miniature pyramids that are heated to a temperature of 385–405 °C. When placed in contact with the skin, the tip creates a thermal effect in the tissue by generating a matrix of coagulation sites (micropores) 200–300 µm deep. The heat is briefly conducted towards the skin (1–2 pulses of 5–18-ms duration) in a controlled manner based on predefined parameters (depth, penetration). The results mimic pulsed energy–based devices such as non-ablative lasers, but the side effects are minor, consisting mainly of mild transient discomfort to the patient, and the downtime is minimal [22].

Considering that the heat transferred can abolish superficial skin lesions and cause dermal coagulation, we sought to determine if the Tixel device might be amenable for use in patients with AKs. The purpose of the current study is to prospectively determine the efficacy and safety of a thermomechanical fractional skin resurfacing technology (Tixel) for treating facial and/or scalp AKs.

Methods

Study design and population

A prospective, open-label, before-after study was performed in a single tertiary medical centre. The primary objective of the present study was to evaluate the efficacy of the Tixel device for the treatment of facial and scalp AKs. The secondary objectives were to evaluate procedure-related safety and subjects' downtime, discomfort, and satisfaction.

The study population consisted of male and female patients aged 18–80 years with skin phototype I–VI who presented with AKs of mild-to-moderate thickness on the scalp and/or face from May 21, 2020, to April 19, 2021. All patients provided written informed consent to participate in the study and were willing and able to comply with the study requirements. The exclusion criteria were conditions that might bias the outcomes or pose a potential risk to patients, as listed in Supplementary Table S1.

Procedure

Initially, demographic and medical history data were collected, and a skin examination was performed. Up to 3 treatments, 3–4 weeks apart, with the Tixel device were applied. Treatment settings included protrusion depth of 400–700 µm, pulse duration of 10–12 ms, and a single pass covering the entire lesions (not the entire face/scalp), to a clinical endpoint of slight erythema. The precise number of treatments was determined by the investigators based on the clinical improvement. Follow-up visits to evaluate the safety and efficacy of treatment were conducted at 4 weeks (±7 days) and 3 months (±7 days) after the last treatment session, for a total of up to 6 clinic visits. The assessment schedule is detailed in Table 1.

Efficacy endpoints

Blinded efficacy assessment Efficacy was measured by the overall mean reduction in AK lesion count, calculated as the difference from baseline, and by the number of patients with an overall improvement in facial/scalp appearance of 26–50% (score 2). Those two primary efficacy outcomes were each assessed by two independent dermatologists (a total of 4 assessors) from photographic images taken at the baseline visit (visit 1) and 3 months after the last visit (visit 5, Table 1). The clinical appearance of the lesions was scored on a quartile scale of improvement, as follows: 0 = exacerbation, 1 = 1–25% improvement, 2 = 26–50% improvement, 3 = 51–75% improvement, or 4 = 76–100% improvement.

Unblinded (comparative) efficacy assessment As opposed to the primary efficacy outcomes, the secondary ones were performed by the unblinded primary investigator based on physical examination (not photographs) throughout the study. At the 3-month follow-up (visit 5), efficacy was measured as follows: overall mean reduction in AK lesion count from baseline and percentage of patients whose lesions were scored 2, 3, or 4.

Safety assessment Adverse effects (AEs) were recorded at each treatment visit (visits 1–3, Table 1). Anticipated treatment-related AEs were irritation, edema, or erythema.

Table 1 Schedule of assessments in 20 patients treated for actinic keratoses with the Tixel

	1 (0)	2 (3–4 W)	3 (6–8 W)	4 (10–12 W)	5 (study end, 5 M)
Evaluation	Sc*/Tx 1	FU/Tx 2	FU/Tx 3	FU	FU
Time from last Tx/visit	0	3–4 W	3–4 W	1 M **(±7 D)**	**3 M (±7 D)**
Inclusion/exclusion criteria	X				
Informed consent	X				
Medical history/medication	X				
Demographic/skin information	X				
Photography	X	X	X	X	X
Treatment	X	X	X		
Subject pain evaluation (VAS)	X	X	X		
Subject satisfaction (questionnaire)					X
Safety evaluation	X	X	X	X	X
Subject downtime evaluation		X	X	X	
Post-treatment AE	X	X	X		
Evaluation of lesion count and improvement by investigator (unblinded)	X	X	X	X	X
Assessor blinded evaluation of lesion count and improvement[†]	X				X

Sc, screening; *Tx*, treatment; *FU*, follow-up; *D*, days; *W*, weeks; *M*, months; *VAS*, visual analogue scale; *AE*, adverse effect

[*]Treatment may be performed on the same day of screening

[†]Primary endpoint. The blinded independent dermatologists performed these assessments 3 months after the last treatment (visit 5)

Patients also self-reported the degree of pain and discomfort associated with the procedure (visits 1–3, Table 1) using a 10-point visual analogue scale (VAS) (0 = no pain to 10 = intolerable pain). Downtime was defined as the period following the procedure (measured in hours or days) during which the patient felt unable/unwilling to go out in public due to edema, erythema, or any other AEs.

Satisfaction assessment At the 3-month follow-up (visit 5, Table 1), patients were asked to complete a satisfaction questionnaire covering the treatment results, the treatment experience, and the fulfilment of expectations. Each parameter was scored on a 5-point Likert scale (0 = very dissatisfied, 1 = dissatisfied, 2 = somewhat satisfied, 3 = satisfied, 4 = very satisfied).

Statistical analysis

Demographic and baseline clinical characteristics were summarized using descriptive statistics. All tests were two-tailed, and a *p*-value of 5% or less was considered statistically significant.

The Clopper–Pearson interval for proportions was calculated for the improvement score by visit and for the satisfaction score at visit 5. The Wilcoxon signed-rank test was applied to test the statistical significance of the change from baseline in number of lesions and VAS pain score and to determine if the difference between the mean clinical improvement achieved at each visit and score 2 was statistically significant.

The intention to treat (ITT) population included all patients who were enrolled and underwent at least one treatment with the study device. Safety analysis was performed on the ITT population. The per-protocol (PP) analysis set consisted of patients who received the full treatment and had qualified photos taken at the 3-month follow-up visit. Primary efficacy analysis was performed on the PP population. Missing values were not imputed.

The data were analyzed using SAS® version 9.4 (SAS Institute, Cary, NC, USA).

Ethical approval

The study was conducted according to ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects and was approved by the Ethics Committee of Rabin Medical Center (approval no. RMC-0714–19).

Results

Study cohort

A total of 20 patients were enrolled in the study, 12 males and 8 females, of mean age 62.9 ± 11.5 years (median 67.5, range 36–74). Five patients had Fitzpatrick skin type I and 15 had Fitzpatrick skin type II. None of the patients had a clinically significant medical history that was relevant to the study. All concomitant medications taken by the patients were initiated to manage comorbidities and were unrelated to the study treatments or AEs. The medical history of the patients is detailed in Table S2.

All 20 patients completed the study, forming the ITT cohort: 19 (95%) completed 3 treatments and 1 completed 2 treatments (as per the primary investigators' decision, due to 100% lesion clearance after the second treatment). One subject had scalp hair growth at the 3-month follow-up which prevented photographic evaluation, limiting the PP population to 19 patients.

Efficacy analysis

The mean number of AKs at baseline evaluated by the two assessors who were blinded to the timing of the photos (before or after treatment) was 9.8 ± 4.9, and the overall mean reduction in the number of lesions was 7.9 (± 4.4), for a rate of 80.6% ($p < 0.0001$). At the 3-month follow-up (visit 5), 18 patients (94.7%) had at least 50% clearance, and 13 patients (68.4%) had at least 75% clearance. Six patients (31.6%) had complete clearance after treatment. Changes over time in the number of lesions and the clearance rates according to each assessor are detailed in Table 2 and Table S3, respectively.

Improvement scores were evaluated by another 2 blinded assessors. The rate of correct identification of the timing of the photographs (i.e., which were taken before treatment and which after) was 94.7% (18 patients) for one and 89.5% (17 patients) for the other. Table 3 depicts the distribution of the improvement scores. The mean improvement score was 2.0 (± 0.8). On the Wilcoxon signed-rank test, there was no significant difference between the average score assigned by the assessors, independently or together, and score 2 (26–50% improvement).

The mean number of AKs at baseline, assessed by physical examination of the unblinded assessor (primary investigator), was 10.1 ± 5.2 and the mean overall reduction in the number of lesions was 8.2 (± 4.7), for a rate of 81.2% ($p < 0.0001$, Table S4). Of the 20 patients analyzed, 18 (90.0%) had at least 50% clearance and 14 (70.0%) had at least 75% clearance at the 3-month follow-up visit. Six patients (30.0%) had complete clearance (Table S5).

The overall improvement in AKs evaluated by the unblinded assessor is shown in Table S6. The mean score at visit 2 (Tx 2) was 2.6 ± 0.9, and it gradually increased

Table 2 Number of AK lesions assessed by blinded assessors and changes in lesion count from baseline

Assessor	*N*	No. of lesions before Tx		No. of lesions at 3-M FU		Change in no. of lesions from baseline		
		Mean	± SD	Mean	± SD	Mean	± SD	*p* value*
Assessor 1	19	9.9	4.9	1.9	2.3	− 8.0	4.4	< 0.0001
Assessor 2	19	9.7	4.8	1.8	2.3	− 7.8	4.3	< 0.0001
Average of the two assessors	19	9.8	4.9	1.9	2.3	− 7.9	4.4	< 0.0001

Tx treatment, *FU* follow-up, *SD* standard deviation

*Wilcoxon signed-rank test

Table 3 Clinical improvement in actinic keratosis assessed by blinded assessors

Assessor	*N*	Improvement score distribution, *n* (%)					Mean improvement score	
		0	Score 1 1–25%	Score 2 26–50%	Score 3 51–75%	Score 4 76–100%	Mean	± SD
Assessor 1	19	1 (5.3)	3 (15.8)	10 (52.6)	4 (21.1)	1 (5.3)	2.1†	0.9
Assessor 2	19	2 (10.5)	2 (10.5)	10 (52.6)	5 (26.3)	—	1.9†	0.9
Average of the two assessors	19						2.0†	0.8

SD, standard deviation

†Confidence intervals: assessor 1 (1.6, 2.5), assessor 2 (1.5, 2.4), both assessors (1.6, 2.4)

over time to 3.6 ± 0.9 at the 3-month follow-up. By the follow-up visits, most of the patients had achieved the highest available improvement score (76–100%, grade 4): 14/20 patients at 4 weeks after the last treatment (visit 4) and 15/20 at 3 months after the last treatment (visit 5). None of the patients demonstrated worsening of the AKs following treatment. Figures 1 and 2 show the before-and-after photos of 2 representative patients.

Safety analysis

No unexpected AEs were observed in any of the patients throughout the study. Most patients had redness, edema, and scabs for 0–2 days after treatments and heat sensation for 0–2 h after treatment. The mean procedure-associated VAS scores (on a scale of 0–10) were as follows: 2.2 ± 1.2 at treatment visit 1 ($N = 20$), 2.2 ± 1.8 at treatment visit 2 ($N = 20$), and 2.5 ± 1.7 at treatment visit 3 ($N = 19$). There was little downtime; all participants reported feeling able and willing to return to work and social activities at ≤ 2 days following each treatment session (Table S7).

Patient satisfaction

On the satisfaction questionnaire completed at the 3-month follow-up visit, most of the patients reported being "very satisfied" overall. Specifically, 11 (55.0%) were very satisfied with the results of the treatment, 15 (75.0%) were very satisfied with the treatment experience, and 12 (60.0%) were very satisfied with the degree to which their expectations were met. The mean scores for each of these parameters on a scale of 1 to 5 were 4.3 ± 1.0, 4.6 ± 0.9, and 4.4 ± 1.0, respectively (Table 4).

Discussion

This study sought to evaluate the efficacy and safety of the Tixel technology for treating AKs of the face and scalp, which are in fact considered, by some, squamous cell carcinoma in situ [5]. All 20 patients enrolled completed the study with minimal anticipated AEs and downtime. Treatment was beneficial by all predefined parameters. The mean overall reduction in the number of lesions as evaluated by the blinded assessors correlated with the findings of the unblinded investigator. Most patients were either very satisfied or satisfied with the treatment results and experience.

It is noteworthy that the Tixel device is mainly used for aesthetic purposes. It was shown to improve skin complexion and attenuate wrinkles [22, 23] by thermomechanical fractional coagulation of the papillary dermis. Dermal coagulation and healing through fibroblast proliferation in

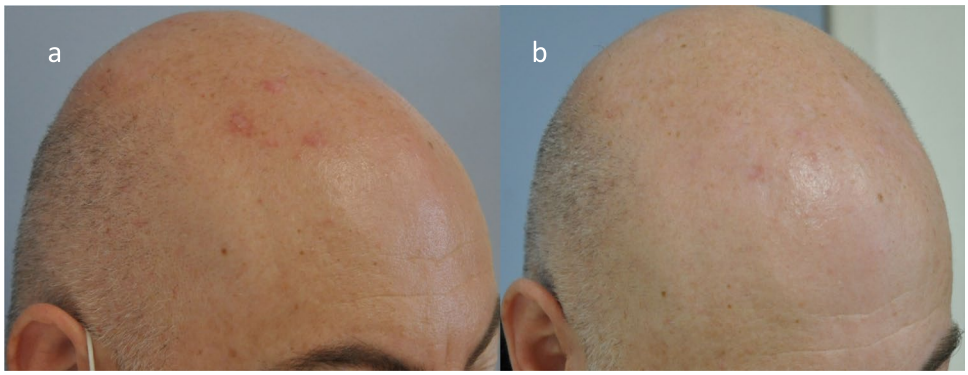

Fig. 1 Representative patient before treatment (**a**) and at the 3-month follow-up (visit 5) (**b**)

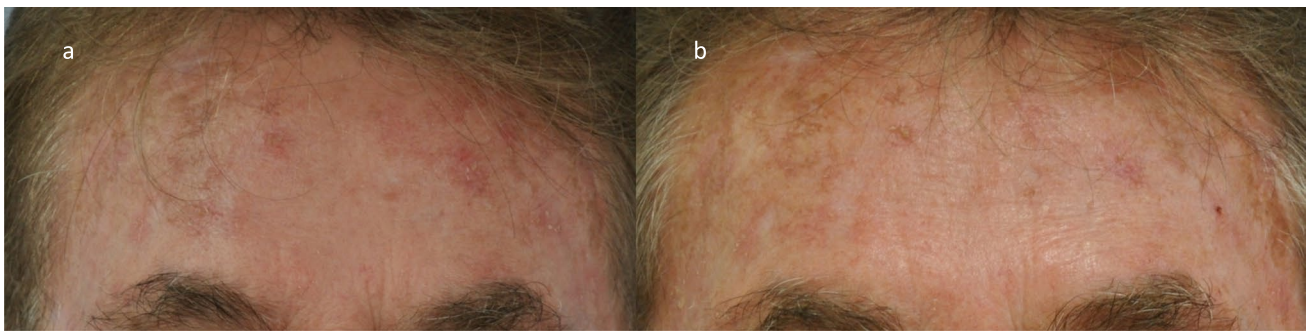

Fig. 2 Representative patient before treatment (**a**) and at the 3-month follow-up (visit 5) (**b**)

Table 4 Responses to satisfaction questionnaire at visit 5, 3 months after the last treatment

Parameters	*N*	%
Results of the treatment		
(1) Very dissatisfied	1	5.0
(3) Somewhat satisfied	2	10.0
(4) Satisfied	6	30.0
(5) Very satisfied	11	55.0
The treatment experience		
(1) Very dissatisfied	1	5.0
(4) Satisfied	4	20.0
(5) Very satisfied	15	75.0
Expectations (the treatment fulfilled the subject's expectations)		
(1) Very dissatisfied	1	5.0
(3) Somewhat satisfied	2	10.0
(4) Satisfied	5	25.0
(5) Very satisfied	12	60.0

the dermoepidermal cleft became apparent 7 days after treatment with the production of new collagen, and skin texture and appearance continued to improve with successive sessions [22].

AKs are epidermal lesions [1], and most of the heat transferred to the dermis by the Tixel device is absorbed by the epidermis [23], leading to the creation of epidermal microcraters. Tixel-induced epidermal microcraters have been found to fully restore as soon as 2 weeks after treatment [24], which explains the minimal skin symptoms, successful rapid wound healing, and minimal downtime observed in this study, in contrast to ablative lasers.

Indeed, it is possible that Tixel-induced improvement in skin aesthetics may have contributed to the patients' satisfaction and to the evaluation of the overall improvement.

Previous studies have shown that Tixel application can also improve drug delivery via the same thermomechanical mechanism. The Tixel has been used for percutaneous drug delivery of aminolevulinic acid for photosensitization [25] or acne vulgaris [26], triamcinolone acetonide and 5-fluorouracil for hypertrophic scars [27], and botulinum toxin type A for rosacea [28]. Thus, besides direct thermal treatment of AKs, the Tixel could potentially aid in increasing the permeability of topicals (such as diclofenac 3% gel or imiquimod), designated to treat AKs. This concept warrants further investigation.

The limitations of the present study include a relatively small sample size, lack of control group, and short follow-up period. Nevertheless, given that this is the first prospective study to evaluate application of the Tixel device for the treatment of AKs, the results obtained are quite compelling. An additional possible limitation is the lack of palpation in the blinded assessment which may have led to an increase in the AK count. However, this shortcoming was compensated by the correlation between the blinded photographic evaluation with the unblinded clinical evaluation. In addition, only fair-skinned individuals were included in the study, but this is the population at highest risk of nonmelanoma skin cancer.

In conclusion, the Tixel device was found to be a relatively efficient and safe modality for the treatment of mild-to-moderate AKs on the scalp and face.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10103-022-03558-4.

Author contribution Assi Levi designed the study and wrote the study protocol.

Meital Oren-Shabtai, Nadezhda Sloutsky, and Assi Levi collected and interpreted data and wrote the first draft of the study.

Moshe Lapidoth, Daniel Mimouni, Igor Snast, Yael Anne Leshem, Rivka Friedland, Ilia Chorny, and Emmilia Hodak collected and interpreted data.

All authors participated in writing the final draft of the paper and had critical input to its final form.

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Data availability All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval The study was conducted according to ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects and was approved by the ethical committee of Rabin Medical Center (RMC-0714–19).

Conflict of interest The authors declare no competing interests.

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