Comprehensive Review of Thermomechanical Fractional Injury Device: Applications in Medical and Cosmetic Dermatology

by BLANCA ESTUPIÑAN MD; ADAM SOUCHIK, MD; ALEXANDRA KISZLUK, BS; and SHRADDHA DESAI, MD

Drs. Estupiñan, Souchik, and Desai are with the Division of Dermatology at Loyola University Medical Center in Maywood, Illinois. Ms. Kiszluk is with the Stritch School of Medicine at Loyola University Chicago in Maywood, Illinois. Additionally, Dr. Desai is with Duly Health and Care Dermatology in Naperville, Illinois and the Division of Dermatology at Rush University in Chicago, Illinois.

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OBJECTIVE: Our aim was to review the current and emerging dermatological applications of the novel thermomechanical fractional injury (TMFI) device, Tixel® (Novoxel, Netanya, Israel). **METHODS:** A systematic review of PubMed using the search terms of "Tixel", "thermomechanical fractional", ["thermomechanical ablation" and "skin"], and ["thermomechanical ablation" and "dermatology"]. **RESULTS:** Thirty-six articles matched our inquiry. Fifteen articles did not meet inclusion criteria. Of the remaining 21 articles, eight were related to device-assisted drug delivery, seven related to photoaging, and seven related to scientific/ preclinical exploration. Preclinical studies have shown ablative and non-ablative microchannel formation similar to that of CO_2 laser but without charring, with clinical studies demonstrating efficacy for a wide range of applications including rhytides, hypertrophic scarring, infantile hemangiomas, and acne/rosacea. The treatment is well tolerated with minimal discomfort and downtime, showing promise for pain-averse and pediatric populations. Few adverse events have been reported, with a high degree of safety demonstrated in all Fitzpatrick types. **LIMITATIONS:** Heterogeneous result reporting among studies. Limited number of randomized controlled trials. **CONCLUSION:** Tixel® is an emerging TMFI device with a wide range of current and potential applications, including device-assisted drug delivery and treatment of rhytides, photoaging, and scars among other conditions. The device has both ablative and non-ablative settings and has been safely used in all Fitzpatrick skin types. Larger and randomized controlled trials are needed to compare this device to current standard of care treatments. **KEYWORDS:** thermomechanical, fractional ablation, Tixel, rhytides, device-assisted drug delivery.

Tixel (Novoxel, Netanya, Israel) is a thermomechanical fractional injury (TMFI) device that gained U.S. Food and Drug Administration (FDA) approval in February 2021 for procedures necessitating ablation and resurfacing of the skin.[1] It features non-ablative and ablative settings and has gained traction in recent years for a variety of dermatologic conditions. The device has a ceramic base that is heated to 400°C which transfers heat to 81 (9x9) blunt, titanium tips in a 10x10mm array that do not pierce the skin.[2] The tips are applied with pulse durations of 5-18ms at a protrusion depth of 100-1000µm. This creates discrete coagulation zones in the target tissue. The device does not have a target chromophore and is theoretically safe in all skin types.

This review aims to highlight therapeutic uses, including off-label indications, of this new, emerging thermomechanical fractional device. We also reviewed studies that investigated the device's ability to increase drug delivery. Given the device's recent approval, it is important to note that there is a lack of randomized controlled trials, and therefore, a systematic review following PRISMA guidelines was conducted with limitations. The purpose of this review is to assess current uses and safety of Tixel and to highlight the need for additional research.

METHODS

A comprehensive search of PubMed of was conducted. The search terms "Tixel", "thermomechanical ablation", ["thermomechanical ablation" and "skin"], and ["thermomechanical ablation" and "dermatology"] were used to identify studies from the years 2009 to 2023. The last search was conducted March 30th, 2023. Inclusion criteria included: 1) English language, 2) use of thermomechanical ablative fractional device (Tixel), 3) original articles, and 4) relevance to dermatology or skin properties. For clinical studies, case series, prospective trials of any size, and retrospective chart reviews were included. Conference abstracts, single case reports, commentaries, and reviews of studies were excluded. Pre-clinical trials must include in-vivo or ex-vivo portions of the study. Outcomes of interest included objective grading scales, physician-reported and patient-reported outcomes, safety data, and pre-clinical data with visualization

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CORRESPONDENCE: Blanca Estupiñan, MD; Email: bestupinan1@gmail.com

of findings (i.e. histology, optical coherence tomography).

All articles were independently reviewed by at least two authors to ensure eligibility criteria were met. Discrepancies were discussed between authors. Each author collected data independently from the divided articles and input data into a shared spreadsheet for review by co-authors. This review aims to examine the skin effects of a thermomechanical ablation fractional device (Tixel) and its current uses. Clinical studies were assessed on effectiveness and safety of Tixel by subjective and objective measures, while pre-clinical studies were assessed on visualization of tissue responses to treatment.

RESULTS

The database inquiries yielded 36 unique articles. Screening of articles by title and abstract eliminated 11 preclinical biomechanical/irrelevant studies, two non-dermatologic clinical studies, one commentary of a clinical study and one review of preclinical data. A total of 21 articles met eligibility criteria (Figure 1).

Rhytides and photoaging. The majority of clinical trials focus on rhytides and photoaging. (Table 1) A total of 303 patients were treated with Tixel for rhytides and rejuvenation, with an additional 20 receiving treatment for facial and scalp actinic keratoses. Treatment areas included the scalp, full face, periorbital, perioral, neck, and décolletage. Fitzpatrick Skin Types I to V were treated. Treatment settings ranged from 6 to 16ms pulse duration and protrusion depth ranged from 400 to 1,000µm. Most studies delivered 2 to 4 treatments with final follow up ranging from 1 to 6 months.

The first published clinical study treated 10 subjects for periorbital and perioral rhytides and another 23 subjects for mild to moderate photodamage.[2] After three treatments, all patients had improvement of photodamage and complexion, and about three quarters of patients had improvement in wrinkles, some having improvement after one treatment. Erythema resolved within three days for most patients, but four to six days if more aggressive settings were used. Microcrusting appeared for some patients at day five. All subjects agreed that no anesthesia was necessary for the treatments. Downtime ranged from 0 to 1 day for over 90 percent of patients.

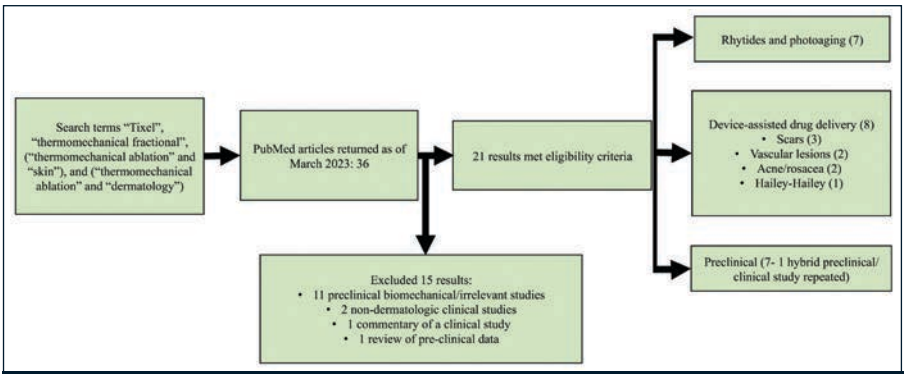

FIGURE 1. Inquiry Results

More recently, a clinical trial with 48 subjects found significant improvement of moderate to severe periorbital rhytides after treating above and below the eyebrow and lower eyelid.[3] Both investigators and three blinded reviewers reviewed final outcomes. All participants responded to treatment with 95.9 percent having a 51 percent or greater improvement on the Global Aesthetic Improvement Scale (GAIS), over half of whom had a 76 to 100 percent improvement. Fitzpatrick Wrinkle Classification System (FWCS) scores demonstrated a significant improvement of rhytides. Patients reported a low level of pain at 2 to 3 out of 10 without topical anesthetic and only optional intraoperative air cooling and post-procedural cold packs offered. Expected erythema and edema lasted three days or less, and subjects were able to return to normal activities in one day or less. The same authors conducted a prospective trial on perioral rhytides in 23 subjects.[4] After four treatments, there was a statistically significant improvement in rhytides and nearly 70 percent improved 76 percent to 100 percent on the GAIS. All patients responded to treatment. Similar to the prior study, only optional air cooling was offered and patients reported a low level of pain, with an average Visual Analogue Scale (VAS) score of 3.1.

A prospective randomized controlled study comparing Tixel to non-ablative fractional (NAFL) 1565nm erbium: glass fiber laser included 68 patients with mild to moderate periorbital rhytides.[5] Three blinded physicians rated outcomes and found a moderate improvement in both treatment arms. Both treatments had a statistically significant improvement in rhytides and there was not a significant difference between the groups. With pre-operative topical anesthetic, the VAS score average was significantly lower in the Tixel treatment arm ($p<0.05$). Microcrusting was present in 52 percent of Tixel and 16 percent of NAFL subjects. There was no difference in resolution of erythema, edema, and downtown time. This study suggests that Tixel is safe and comparable to NAFL in the treatment of periorbital rhytides but is better tolerated.

One group retrospectively reviewed 24 patient cases, including six with Fitzpatrick Skin Type IV+, who underwent two to three Tixel treatments at about one month intervals.[6] By rating photographs, reviewers appreciated improvements in rhytides, pore size, pigmentation, erythema, laxity, and overall complexion. Erythema lasting 3 to 6 days was present in three patients. One Fitzpatrick Type III patient who received higher settings with a protrusion depth of 800µm and 14ms pulse duration with more passes had hyperpigmentation, which resolved with bleaching agents. Average downtime was less than two days. A larger retrospective study assessing safety and tolerability of Tixel included 150 patients with photoaging or acne scarring.[7] Areas treated included the face, including periorbital and perioral areas, neck, and décolletage. The majority of treatments had higher settings with protrusion of 700 and 1,000µm and pulse durations of 14ms. Of note, 39 Fitzpatrick Type IV and 16 Fitzpatrick Type V subjects received 10-14ms pulse durations. Out of the 327 total treatments, there were only two cases of hyperpigmentation, both in Asian patients with Fitzpatrick Skin Type IV. They had higher settings with pulse duration of 14ms and protrusion of 700 or 1,000µm. Fortunately, the pigmentation self-resolved in three months without intervention.

Tixel was also used to treat scalp and facial

TABLE 1. Rhytides and photoaging clinical studies.

FIRST AUTHOR/ YEAR (REFERENCE)	TREATED CONDITION	N/PATIENT DEMOGRAPHICS	SETTINGS/ADJUNCT TREATMENTS	TREATMENT PROTOCOL	RESULTS	ADVERSE EVENTS	OCEBM LEVEL OF EVIDENCE
Elman 2016[2]	• Rhytides and photoaging • 2 treatment groups: Group 1- periorbital rhytides, Group 2- photoaging	Group 1: • 8 patients • Age: 42-65 years • FT: II-IV Group 2: • 18 patients • Age: 50-75 years • FT: II-IV	Group 1: • D tip (high thermal conductivity/ ablative)- Contact interval 14ms single pulse or 9ms double pulse; S tip (low thermal conductivity/non-ablative)- Contact interval 9ms • Unspecified protrusion Group 2: • D tip or S tip: 9-16 ms single pulse • Unspecified protrusion	Group 1: • 3 treatments • 35 day treatment interval • F/u 1-6 months post final treatment Group 2: • 3 treatments • 1-2 month treatment interval • F/u at 1-2 months and 3-4 months post final treatment	Groups 1 and 2: • Average of 75% reduction in rhytides • Average VAS of 3.1 • Average downtime of 0.16 days • 75% of patients rated as "satisfied" or "very satisfied"	HSV reactivation n=1	4
Daniely 2021[6]	Photoaging/ facial rejuvenation	• 24 patients • Age: 39-69 years • FT: II-V	• Contact interval 8-14ms • 500-1000µm protrusion • Single or double pass	• 2-3 treatments • 3-5 week treatment interval • F/u 3 months post final treatment	• Average improvement (-1 to 4 scale †): skin complexion 2.1 +/- 0.49 periorbital wrinkling 2.1 +/- 0.65 "vitality" (vivid/ luminous/healthy skin) 1.7 +/- 0.49 pigmentation and tone 1.4 blood vessels and erythema 1.2 pore size 1.0 wrinkles and laxity 1.0 • Patient reported averages (0 to 5 scale‡): skin improvement of 3.6 (SD 1.2), average treatment experience of 3.9 (SD 1.3), and average fulfillment of expectations 3.4 (SD 1.5)	Post-inflammatory hyperpigmentation n=1	4
Judodihardjo 2022[7]	• Photodamage, acne scars • Retrospective review of TMFI safety in single center	• 150 patients • Age: 20-82 years • FT: I-V • Décolletage, face, neck	• Contact interval 5-14ms • 400-1000µm protrusion • Topical lidocaine/ tetracaine 7%/7% cream applied pre-treatment if contact interval of 8ms or more was utilized • Double pulse utilized if treating acne scarring or skin laxity	• Up to 6 treatments (average 2.16) • 4-6 week treatment interval • F/u 4-6 weeks after primary treatment, non-mandatory	• 2 Asian FT IV patients developed post-inflammatory hyperpigmentation 3 weeks post procedure, both had contact interval of 14ms • 1 patient developed impetigo 2 days post procedure, had contact interval of 14ms • 1 patient developed likely contact dermatitis after applying an over the counter anti-aging cream 3 days post procedure	Post-inflammatory hyperpigmentation n=2, impetigo n=1, dermatitis n=1	4

TABLE 1. (CONTINUED) Rhytides and photoaging clinical studies.

FIRST AUTHOR/ YEAR (REFERENCE)	TREATED CONDITION	N/PATIENT DEMOGRAPHICS	SETTINGS/ADJUNCT TREATMENTS	TREATMENT PROTOCOL	RESULTS	ADVERSE EVENTS	OCEBM LEVEL OF EVIDENCE
Oren-Shabtai 2022[8]	• Actinic keratoses	• 20 patients • Age: 18-80 years • FT: I-II	• Contact interval 10-12ms • 400-700µm protrusion	• Up to 3 treatments • 3-4 week treatment interval • F/u 1 and 3 months post final treatment	• Average blinded reduction in lesion count of 80.6%±* • Average unblinded reduction in lesion count of 81.2%*± • Average VAS of 2.2-2.5 at each treatment • Average patient treatment satisfaction of 4.3 +/- 1.0, experience satisfaction of 4.6 +/- 0.9 (5 point scale)	None	4
Salameh 2022[5]	• Photoaging/ facial rejuvenation • TMFI vs. NAFL (Erbium:glass 1565nm)	• 68 patients (34 TMFI group, 34 NAFL group) • Age: 40-70 years • FT: I-VI	TMFI: • Contact interval 10ms • 500µm protrusion NAFL: • 150-300/cm^2 treatment density • 8-17mm scan size (mean 21mm) • 13-25mJ energy (mean 21mJ) Both groups: • Unspecified pre-operative anesthetic cream	• 3-5 treatments • 3-5 week treatment interval • F/u at 1, 3, and 6 months post final treatment	Average improvement in FWCS: • TMFI 1.6 +/- 0.6* • NAFL 1.7 +/- 0.8* • No statistical difference in efficacy between treatments Average VAS: • TMFI 4.01 +/- 2.6 • NAFL 5.83 +/- 2.3	• TMFI: dry or watery eyes n=2 • NAFL: uveitis n=1 (unrelated to treatment)	2
Wang 2023[3]	• Periorbital rhytides	• 48 patients • Age: 38-70 years • FT: I-IV	• Contact interval 8-12ms • 400-600µm protrusion • Single or double pass • Intra-operative air cooling offered	• 4 treatments • 3-5 week treatment interval • F/u 3 months post final treatment	• Average FWCS improvement of 2.04 +/-0.58* • Average GAIS score 3.52/4 (+/-0.58) • Average VAS at each treatment of 2.81-2.98 • 93.8% satisfied with results; 95.8% satisfied with treatment experience	Erythema n=1, back pain n=1 (unrelated)	4
Wang 2023[4]	• Perioral rhytides	• 23 patients • Age: 53-72 years • FT: I-IV	• Contact interval 6-12ms • 500-800µm protrusion • Double pass • Intra-operative air cooling offered	• 4 treatments • 3-5 week treatment interval • F/u 1 and 3 months post final treatment	• Average FWCS improvement of 1.7 at 1 month* and 1.9 at 3 months* • Average GAIS score 3.4/4 at both 1 and 3 months • Average VAS at each treatment 3.0-3.4 • 73.9% satisfied with results at 3 months; 91.3% satisfied with treatment experience at 3 months	None	4

OCEBM, Oxford Centre for Evidence-Based Medicine ; FT, Fitzpatrick skin type; VAS, visual analog scale; TMFI, thermo-mechanical fractional injury; NAFL, non-ablative fractional laser; FWCS, Fitzpatrick wrinkle classification system; SD, standard deviation; GAIS, global aesthetic improvement scale; *$p < 0.0001$

† 6 point scale: -1= worsening, 0= no change, 1= 0-25% improvement, 2= 26-50% improvement, 3= 51-75% improvement, 4= 76-100% improvement

‡ 5 point scale: 0= worsening, 1= 0-25% improvement, 2= 26-50% improvement, 3= 51-75% improvement, 4= 76-100% improvement

TABLE 2. Device-assisted drug delivery clinical studies.

FIRST AUTHOR/ YEAR (REFERENCE)	TREATED CONDITION	N/PATIENT DEMOGRAPHICS	SETTINGS/ADJUNCT TREATMENTS	TREATMENT PROTOCOL	RESULTS	ADVERSE EVENTS	OCEBM LEVEL OF EVIDENCE
Scars							
Artzi 2019[9]	Keloid scars	• 7 patients • Age: 4-55 years • FT: II-IV	• Contact interval 5-8 ms • 1000µm protrusion • Kenalog 40mg/mL and 5-fluorouracil 50 mg/mL mixed 1:9 ratio	• 8 treatments • 2-3 week treatment interval • F/u 2-3 month post final treatment	• Mean keloid VSS decreased from 8.6 +/- 1.2 to 5 +/- 2.7* • Mean pain VAS score 2.5 +/- 0.7 • Patient/guardian satisfaction rated as moderate-high • 1 patient did not respond to treatment	None	4
Artzi 2020[10]	Pediatric hypertrophic burn scars	• 4 patients • Age: 3-10 years • FT: II	• Contact interval 5-8ms • 1000µm protrusion • Kenalog 40mg/mL and 5-fluorouracil 50mg/mL mixed 1:9 ratio • Post-topical sonophoresis	• 8 treatments • 2-3 week treatment interval • F/u 1 month post final treatment	• Mean VSS reduction from 8.4 +/- 0.8 to 5.2 +/- 0.5* • Mean pain VAS score 1.74 +/- 0.9 • Patient guardians rated satisfaction as moderate-high	None	4
Manuskiatti 2022 [11]	• Hypertrophic scars • Split-scar comparison of TMFI + topical triamcinolone 10mg/mL vs. Intralesional triamcinolone 10mg/mL	• 21 patients • Age: 22-55 years • FT: III-IV	• Contact interval 10ms • 400µm protrusion • Intra-operative cooling utilized • Topical triamcinolone 10 mg/mL	• 5 treatments • 1 month treatment interval • F/u 6 months post final treatment	• Mean VSS: TMFI decreased from 6.61 +/- 1.82 to 2.28 +/- 1.70*; • ILT decreased from 6.57 +/- 2.11 to 2.52 +/- 1.83* • Mean pain VAS scores: TMFI 3.13 +/- 1.84; ILT 4.79 +/- 2.11* • All patients preferred treatment experience and outcomes of TMFI compared to ILT	• TMFI: None • Intralesional triamcinolone: skin atrophy n=10, telangiectasia n=1, post-inflammatory hyperpigmentation n=2	2
Vascular lesions							
Mashiah 2020[12]	Infantile hemangioma	• 11 patients • Age: 1.5-16 months • FT: unspecified	• Contact interval 6ms • 400µm protrusion • Either propranolol 4% PLO or timolol 0.5% ophthalmic solution applied 4 times at 1 hour intervals post TMFI • 3 patients also applied topical propranolol PLO BID at home for first month of treatment • 4 patients began with propranolol PLO and switched to timolol	• 3-9 treatments • 2-4 week treatment interval • F/u 3 months post final treatment	• 7 patients with good response[#†] • 4 patients with partial response[#†]	None	4

TABLE 2. (CONTINUED) Device-assisted drug delivery clinical studies.

FIRST AUTHOR/ YEAR (REFERENCE)	TREATED CONDITION	N/PATIENT DEMOGRAPHICS	SETTINGS/ADJUNCT TREATMENTS	TREATMENT PROTOCOL	RESULTS	ADVERSE EVENTS	OCEBM LEVEL OF EVIDENCE
Vascular lesions							
Artzi 2020[13]	• Port wine stains • Split-lesion comparison of TMFI + rapamycin 0.2% cream + PDL vs. rapamycin 0.2% cream + PDL	• 3 patients • Age: 10-16 years • FT: II-III	• Contact interval 6ms • 400µm protrusion • Rapamycin 0.2% cream BID and immediately post TMFI • PDL treatment every 4-6 weeks for both sides of scar	• 6-9 treatments • 2 week treatment interval • F/u 4 weeks post final treatment	• Physician average rating of 51-75% improvement in TMFI side, 0-50% improvement in the non-TMFI side • Patient average rating of 25-75% improvement in TMFI side, < 25% improvement in the non-TMFI side • No difference in patient tolerance between sides	Both sides of scar: Transient post-inflammatory hyperpigmentation n=1, erythema + crusting n=2 (resolved after rapamycin withdrawal + topical steroid)	4
Other							
Friedman 2019 [14]	Rosacea	• 16 patients • Age: 23-45 years • FT: II-IV	• Contact interval 6-8ms • 800-1000µm protrusion • Topical 100U abobotulinumtoxin • Post-topical sonophoresis • Trolamine cream TID for 2 days post procedure	• 2 treatments • 1 month treatment interval • F/u 1, 3, and 6 months post final treatment	• Positive Demodex folliculorum cultures decreased from 9 to 4 patients • CEA improved from 2.81 +/- 0.93 to 1.12 +/- 0.44, 1.24 +/- 0.64, and 1.87 +/- 0.75 at 1, 3, and 6 months* • PSA improved from 3.03 +/- 1.1 to 1.03 +/- 0.58, 1.09 +/- 0.78, and 1.81 +/- 0.84 at 1, 3, and 6 months* • Average Mexameter scores at baseline, 1, 3, and 6 months were 399.12, 211.18, 236.25, and 299.62* • Average DLQI improved from 18.6 +/- 1.9 to 9.6 +/- 2.8 at 6 final f/u* • Well tolerated	None	4
Hilerowicz 2020[15]	Acne	• 30 patients • Age: 16-59 years • FT: II-IV	• Contact interval 6ms • 400-600µm protrusion • 5% ALA gel 1 hour incubation, then red light (630nm) from non-coherent light source at 60 J/cm^2 for 12 min and 47 sec • In the second and third treatments, incubation time was increased by 15 min and light dose by 5 J/cm^2	• 1-3 treatments • 1 month treatment intervals • F/u 8 and 16 weeks post final treatment	• 26.7% and 23.7% reduction in AGSS at 8 and 16 weeks • 65.2% and 60.6% improvement in Leeds score at 8 and 16 weeks • Overall response rate: 3.3 +/- 0.5 /4 • PGIC score of 5.5/7	Prolonged erythema (mean 12.4 days)	4

TABLE 2. (CONTINUED) Device-assisted drug delivery clinical studies.

FIRST AUTHOR/ YEAR (REFERENCE)	TREATED CONDITION	N/PATIENT DEMOGRAPHICS	SETTINGS/ADJUNCT TREATMENTS	TREATMENT PROTOCOL	RESULTS	ADVERSE EVENTS	OCEBM LEVEL OF EVIDENCE
Other							
Bar-Ilan 2020[16]	Hailey-Hailey disease	• 8 patients • Age: 31-57 years • FT: II-III	• Contact interval 6-8ms • 400-600µm protrusion • 125-250U botulinum toxin Type A • Post-topical sonophoresis	• 2 treatments • 4-6 week treatment interval • F/u 6-8 week	• Average PGA of 1.75 • Remission for average of 2.875 months • Treatment response for average of 7.125 months • Average DLQI improvement of 8.88 • Average VAS of 2.5	None	4

OCEBM, Oxford Centre for Evidence-Based Medicine; FT, Fitzpatrick skin type; VSS, Vancouver scar scale; VAS, visual analog scale; TMFI, thermo-mechanical fractional injury; ILT, intralesional triamcinolone; PLO, pluronic lecithin organogel; PDL, pulsed dye laser; CEA, clinicians erythema assessment; PSA, patient self assessment; DLQI, dermatology life quality index; ALA, aminolevulinic acid; AGSS, acne grading scoring system; PGA, physician global assessment; *p-value < 0.001

† Response graded on 4 physician rated categories, each on a 0-3 scale, then scores were averaged, Categories: size regression, lightening of surface color, flattening, deep component reduction, Scores: 0-1= poor, 1.1-2= partial, 2.1+ = good response

actinic keratoses with mild to moderate thickness in a prospective trial of 20 patients.[8] There was a decreased lesion burden after 2 to 3 treatments as evaluated by blinded and unblinded evaluators. At final follow up three months after treatment, 75 percent of patients had 76 to 100 percent improvement. Regarding side effects, redness, edema, and scabs were noted for 0 to 2 days and there were no adverse events. The treatment was well tolerated with a low level of pain and subjects were able to return to activities in two days or less.

Device-assisted drug delivery. Study design, treatment protocols, and key findings for device-assisted drug delivery studies are summarized in Table 2.

Scars. Regarding treatment of scars, treatment sites included the trunk and extremities and there were no adverse events, including in Fitzpatrick Type IV patients. Typically, a protrusion of 1,000µm and pulse duration of 5-10ms was utilized. Treatments ranged from 5 to 8 sessions over 2 to 4 week intervals. Final follow up ranged from 1 to 6 months. Two studies on hypertrophic and keloid scars including a pooled total of 11 patients, aged as young as three years old, found Tixel-assisted drug delivery of 1:9 triamcinolone 40mg/mL: 5-fluorouracil 50mg/mL to be effective in improving scar quality.[9,10] Mean Vancouver Scar Scale (VSS) scores improved significantly and patients (or their guardians) were highly satisfied with the treatment experience. There was one non-responder and no adverse events occurred. One split-scar study comparing Tixel-assisted triamcinolone 10mg/mL delivery to standard intralesional triamcinolone found comparable outcomes in scar improvements.[11] The Tixel treatment arm was better tolerated and preferred by patients and did not result in adverse events as seen with the intralesional steroid. Further split-scar studies are needed to compare Tixel to standard of care scar treatments.

Vascular lesions. A retrospective study included 11 patients with infantile hemangiomas on the head, neck, and extremities that were treated with Tixel-assisted delivery of timolol 0.5% eye drops and/or a propranolol 4% gel.[12] Tixel was used with a protrusion of 400µm and pulse duration of 6ms and delivered over a series of 4 to 9 treatments. Based on grading of size regression, color lightening, flattening, and deep component reduction, all patients had "good" or "partial" response to treatment. None had "poor" or "no response". Of note, a large 20 x 6cm and other substantially thick hemangiomas had a "good" response to treatment. No recurrence of lesions or systemic or local adverse events occurred. The authors noted that with an average of 5.5 treatments and total duration of 17 weeks, the addition of Tixel-assisted drug delivery provides a shorter treatment course compared to the standard 5 to 7.5 months of beta-blocker monotherapy.

In one case series, three pediatric patients with port wine stains, who had insufficient response to pulsed dye laser treatments, underwent Tixel-assisted drug delivery of rapamycin.[13] Half of each lesion received 595-nm pulsed dye laser, Tixel 2 to 14 days later, and topical rapamycin 0.2% cream immediately after Tixel and twice daily. The other half was treated with pulsed dye laser and rapamycin 0.2% cream only. Investigators found that the Tixel-treated halves had a higher clearance rate and patients were more satisfied with the outcome. There was no difference in side effects between treatment arms.

Acne and rosacea. For treatment of resistant rosacea facial flushing, 16 patients underwent Tixel-assisted abobotulinumtoxin A delivery. (14) Patients underwent two treatments of Tixel at 800-1,000µm protrusion with 6-8ms pulse durations, followed by topical application of 100 units of botulinum toxin diluted in saline, applied with sonophoresis. Both clinician and patient assessments of erythema at baseline were around a "moderate" grading, which improved to an "almost none" to "mild" grading at 1, 3, and 6 months post-treatment. This effect was also demonstrated with Mexameter measurements, which significantly improved as well. Additionally, Demodex cultures were significantly reduced and quality of life scores significantly improved. The treatment was well tolerated.

TABLE 3. Preclinical studies

FIRST AUTHOR/ YEAR (REFERENCE)	STUDY AIM	TEST SUBJECTS	SETTINGS/OTHER PARAMETERS	TREATMENT PROTOCOL	RESULTS	ADVERSE EVENTS
Lask 2012[17]	Scientific exploration of TMFI with Tixel pre-cursor "ThermiXel"	Cadaveric porcine abdominal skin	• 10 x 10 rod array in this prototype • 400°C rod treatment temperature • Contact interval 2.5ms • 50-250µm protrusion • Skin chilled to 14°C with ice prior to treatment	• Single pulse • Microscopically examined under H&E	• Vaporization crater of 200µm depth and 380 µm width • Thermal collateral damage zone of 80µm laterally and 250µm in depth (in a 100µm wide cone configuration) • No charring noted	N/A
Sintov 2016[18]	• In-vitro exploration of penetration of topical preparations after TMFI • Also evaluation of patency of microchannel through phenol-red dye visualization under confocal microscopy, both in-vitro and in-vivo	In-vivo group: • 6 human patients • Age: 31-61 years • Unspecified FT, noted to be "Caucasian" • Only channel patency explored In-vitro group: • Cadaveric porcine ear skin • Both channel patency and drug delivery assessed	Channel patency trials: • Contact interval 8-9ms • 400µm protrusion • Phenol-red dye Drug delivery trials: • *Verapamil*: Contact interval 6ms and 9ms • *Diclofenac:* Contact interval 8ms • *Magnesium ascorbyl*: Contact interval 8ms • All drug delivery trials with 400µm protrusion	Channel patency: • Phenol-red dyed microchannels evaluated at 0, 2, and 6 hours both in-vivo and in-vitro Drug delivery: • Accomplished with Franz diffusion cell system and chromatography hourly for 6 hours	Channel patency: • Channels remained open for at least 6 hours after TMFI • Hydrophilic dye appeared to have increased penetration at hour 6 compared to hour 0 (immediately post treatment) Drug delivery: • *Verapamil*: Permeability increased ~10x and ~20x for 6ms and 9ms contact intervals, respectively • *Diclofenac*: Permeability increased ~3x • *Magnesium ascorbyl*: Permeability co-efficient increased from 0in untreated to 2.02x10-4 +/-0.49x10-4cm/h in TMFI treated skin	None
Elman 2016[2]	• Exploration of crater characteristics of TMFI vs. CO_2 laser • Comparison of D (high thermal conductivity/ ablative) and S (low thermal conductivity/ non-ablative) tips	• 2 male volunteers, forearm skin • 7 in vivo porcine models, flank skin	• "A range of parameters" used for TMFI • Volunteers also treated with CO_2 laser	• Volunteers were biopsied immediately after treatment • Porcine models were biopsied immediately after treatment and at 1 week after treatment	• D tip showed ablation with coagulation of the papillary dermis similar to CO_2 laser, although half the width of CO_2 laser craters • S tip showed no ablation but epidermal vacuolization with coagulation of the papillary dermis, except on low settings where no dermal coagulation was seen • Delayed porcine biopsies showed normal healing at 7 days	None
Shavit 2020[19]	In-vivo exploration of drug penetration after TMFI: commercial 20% ALA hydroalcoholic solution, compounded ALA gel†, commercial 10% ALA microemulsion gel, and commercial 16.8% MAL cream	• 5 patients • Age: 35-65 years • FT: II-III • Flexor forearms	• 4 settings utilized: • 5ms contact interval, 700µm protrusion • 6ms contact interval, 400µm protrusion • 8ms contact interval, 400µm protrusion • 10ms contact interval, 400 µm protrusion	• Single pulse • Protoporphyrin IX fluorescence measured • Readings at hourly for 5 hours	• Drug delivery for compounded ALA gel increased linearly across all groups over 5 hours, best penetration increase with 6 ms x 400um protrusion, rate increased 156-176%/hour at this setting over control • No statistically significant increase for the other formulations • Hypothesized to be due to the compounded ALA gel vehicle's adherence to the stratum corneum and relatively low viscosity	None

TABLE 3. (CONTINUED) Preclinical studies.

FIRST AUTHOR/ YEAR (REFERENCE)	STUDY AIM	TEST SUBJECTS	SETTINGS/OTHER PARAMETERS	TREATMENT PROTOCOL	RESULTS	ADVERSE EVENTS
Kokolakis 2020[20]	Exploration of wound healing after TMFI	• 6 patients • Age: 32 (SD 3.8) years • FT: I-III • Dorsal forearms	• Contact interval 12ms • 600µm protrusion	• Single pulse • Evaluated via confocal laser scanning microscopy at day 1, 2, 7, and 14	• Average VAS of 4 +/- 1.9 • Granulation began after 1 day • Upper epidermis re-epithelialized by Day 7 • Complete regeneration of upper epidermis, DEJ, and upper dermis by Day 14	None
Foged 2021[21]	In-vivo exploration of drug penetration after TMFI, pretreatment with compounded 20% ALA cream‡ and compounded 20% ALA gel§	• 12 patients • Age: 18-25 years • FT: I-III • Upper back	• Contact interval 6ms • 400µm protrusion • Pre-treatment with 125µg ALA cream or ALA gel for up to 3 hours	• Single pass • Protopophyrin IX fluorescence measured • Readings every 30 minutes until 3 hours post TMFI • Punch biopsies taken at 3 hour mark, evaluated by protopophyrin IX fluorescence microscopy	• TMFI treatment increased ALA gel penetration 48-136% and ALA cream penetration 20-44% at 3 hours • ALA cream achieved higher skin surface concentration in non-TMFI treated skin • TMFI treatment increased ALA cream penetration of the epidermis 43.6% but did not increase ALA gel penetration • TMFI treatment did not increase either ALA cream or gel penetration to the dermis • Average VAS of 3 • Differences in cream vs. gel hypothesized to be due to increased partitioning of hydrophilic ALA from hydrophobic cream vehicle, as well as cream inclusion of cetrimide	2 participants developed post-inflammatory hyperpigmentation in all areas where ALA was applied including control areas
Wang 2022[22]	Exploration of novel use of optical coherence tomography in confirming microchannels for 7 devices, with extrapolation to usefulness in energy-based device assisted drug delivery	• 1 patient • Upper arm • Unspecified demographics	• Contact interval 6ms • 4µm protrusion	• Single pass • Evaluated via optical coherence tomography immediately post procedure and at 24 hours	• TMFI created channels of 236 µm in width • Channels remained patent at 24 hours post procedure • TMFI was the only non-laser device to demonstrate detectable channels at 24 hours	None

TMFI, thermo-mechanical fractional injury; FT, Fitzpatrick skin type; ALA, aminolevulinic acid; MAL, methyl aminolevulinate; SD, standard deviation; VAS, visual analog scale; DEJ, dermoepidermal junction
† Potassium sorbate 0.2%, oleic acid 10%, sepigel 305 10%, purified water ~59%, and hydrochloric acid 10% solution/potassium hydroxide 15% solution
‡ Per 100 g cream vehicle: 700 mg cetrimide, 5 g glycerol 85%, 8 g cestosteryl alcohol, 40 g paraffin liquid in purified water
§ Per 100 g gel vehicle: 5.9 g glycerol, 0.6 g benzalkonium chloride, 0.3 g disodium edetate, and 1.8 g carmellose sodium in purified water

As an adjunct to photodynamic therapy for acne, Tixel-assisted drug delivery of aminolevulinic acid 5% gel was used on 30 patients, including pediatric patients and Fitzpatrick Types II-IV.[15] Treatment was delivered with a protrusion of 400-600µm and 6ms pulse duration. Next, the gel was applied on the face under occlusion for one hour and then exposed to 630nm red light. After an average of about two treatments, the burden of inflammatory lesions, overall lesions and erythema improved and sustained benefit was appreciated at 16 weeks after the final treatment. Patients reported high satisfaction and low VAS pain scores (average 3.3), though half of patients had prolonged erythema lasting almost two weeks. Average downtime was less than one week.

Hailey-Hailey disease. Given botulinum toxin's effects on decreasing sweat production and potential resultant decrease in microorganism overgrowth, one group studied Tixel-assisted botulinum toxin delivery in eight patients with biopsy-confirmed Hailey-Hailey disease.[16] After Tixel treatment, 125-250 units of botulinum toxin A diluted in saline was applied with sonophoresis. Findings were promising with 7/8 patients having a good or partial response at 6 to 8 weeks after treatment and significantly improved Physician Global Assessment (PGA) and Dermatology Life Quality Index (DLQI) scores. Recurrence occurred an average of seven months and up to one year after treatment and all treatment sites showed similar effectiveness.

There were no systemic or local side effects.

Preclinical studies. Preclinical and proof of concept studies have demonstrated mechanistic justification for clinical findings. (Table 3) Multiple studies have shown TMFI ablation zones ranging from 100-380 microns in width and 100 to 180 microns in depth, with coagulation zones roughly 460 microns in width and 250 microns in depth, depending on settings used. Ablative settings cause vaporization of the stratum corneum. However, on non-ablative settings, the stratum corneum becomes desiccated and "cracked". These changes last at least 24 hours. Due to these phenomena, drug delivery is enhanced with both ablative and non-ablative settings, with increasing levels of drug penetration demonstrated up to six hours post-TMFI. The concomitant dehydration of tissue in the coagulation zone enhances the penetration of hydrophilic compounds, as osmotic flux into the skin is increased. Microchannels occupy roughly 2 percent of the treatment area, allowing for rapid scar-free healing, which has been demonstrated to be complete via confocal laser scanning microscopy after two weeks.[2,17–22]

CONCLUSION

With versatile settings, Tixel has been utilized for a variety of cosmetic and medical dermatologic indications. Tixel-assisted drug delivery studies typically used pulse durations under 10 ms, with all but one study utilizing 5-8 ms. For protrusion, scars were treated with 400 or 1000 µm, rosacea with 800-1000 µm, and vascular lesions, acne and Hailey-Hailey disease with 400 µm. Aesthetic studies included a wider range of settings, considering sensitive areas such as the periorbital region were treated, but pulse durations of up to 14 ms and protrusions of 400-1000 µm were used. Longer pulse durations result in more thermal transfer and deeper dermal coagulation, resulting in more neocollagenesis. Thus pulse durations of >10 ms may be more suited for rhytides, while shorter pulse durations are best for drug delivery.

Some authors have postulated that double passes with moderate settings (i.e. 600 µm, 12 ms) have an estimated treatment density of 15% which may increase downtime and pose a higher risk of adverse events, while another study found hyperpigmentation to occur after a 14 ms pulse duration and protrusion depth of 700 µm and higher were utilized. (6,7) To be cautious, more aggressive settings (i.e. pulse durations >10ms), especially with multiple passes should be used with caution in higher Fitzpatrick Skin Types given the risk of hyperpigmentation. Of note, the device does not have a target chromophore, and thus may be overall safer than some lasers in skin of color.

Given the challenge of both dynamic and static wrinkles in the periorbital and perioral regions, it is promising that multiple trials using Tixel have found clinically meaningful improvement. In addition, the perioral area has been associated with persistent dyschromia, which did not occur in any study.[23] Both the thin, delicate periorbital skin and neck, containing less pilosebaceous units, carry a higher risk of scarring, which was also not reported in any study.[24,25]

All studies exhibited a low level of pain, most without topical anesthesia, which is not only of benefit to the patient but also shortens clinic visits. Aside from the study on photodynamic therapy for acne, downtime was typically less than two days with many patients returning to activities in less than one day. Transient side effects included erythema, edema, and microcrusting and only rare cases of hyperpigmentation were reported. The device features self-sterilizing tips, thus eliminating the cost of tip replacements as seen with other energy-based devices. Despite a logical concern of soft tissue infection, there was only one case of mild impetigo reported.

When comparing Tixel to other well-established energy-based devices in the dermatologist's armamentarium, the ablative capacity of the device is comparable to the fractional carbon dioxide laser in regards to improvement of rhytides and photoaging, but with significantly less pain, side effects, and downtime. Non-ablative settings are similar to the 1565nm erbium: glass laser and likely similar to 1550nm models as well, but treatment discomfort is reduced. The compact design, versatility and safety of the device combined with positive patient reviews and tolerability make Tixel a favorable option.

In general, there is a need for larger studies and randomized, controlled blinded trials. Limitations of this review include variability in grading scales, making comparisons difficult, as well as studies with smaller sample sizes and retrospective analyses. Tixel-assisted drug delivery has been proven useful for several medical conditions. Future studies can explore the use of other topicals such as cosmeceuticals in enhancing skin quality, minoxidil or 5-alpha reductase inhibitors for alopecia, and imiquimod or 5-fluorouracil for actinic damage. Other aesthetic directions could include hand rejuvenation, skin laxity, and Mohs surgery scarring.

In summary, Tixel is a novel energy-based device with promising results for a variety of dermatologic conditions as demonstrated by the studies included in this review.

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