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ORIGINAL CONTRIBUTION

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A new approach in the treatment of pediatric hypertrophic burn scars: Tixel-associated topical triamcinolone acetonide and 5-fluorouracil delivery

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Abstract

Background: Pediatric hypertrophic burn scars are challenging to treat due to their widespread nature and pain associated with the treatment. Intralesional triamcinolone acetonide (TAC) injection with or without 5-fluorouracil (5FU) is considered first-line treatment for severe hypertrophic scars. The pain associated with the procedure, the uneven topography, and epidermal atrophy, all limit the application of this treatment modality.

Aims: We sought to evaluate the clinical effectiveness and safety profile of a novel thermomechanical system (Tixel, Novoxel) for transdermal delivery of a topical solution containing TAC and 5-FU in the treatment of hypertrophic scars.

Patients/Methods: A retrospective study of pediatric hypertrophic burn scars treated between 2015 and 2017 was performed. Epidemiologic, treatment data, effectiveness score, and safety were reviewed.

Results: Four children (one male and three females, ages 3-10 years old) with hypertrophic burn scars treated with the Tixel device were evaluated. Mean scar VSS was reduced from 8.4 ± 0.8-5.2 ± 0.5 (*P*-value – .001) after eight treatments. The mean improvement of toughness, thickness, color, and general aesthetic impression was 3.1 ± 0.43 → 2.2 ± 0.31, 3.4 ± 0.5 → 1.9 ± 0.63, 2.7 ± 0.21 → 2.4 ± 0.25, and 3.23 ± 0.44 → 1.6 ± 0.64, respectively. Mean treatment pain VAS score was 1.74 ± 0.9. Patient's parents rated their satisfaction level as "moderate-high." No topical or systemic complications were observed.

Conclusion: Thermomechanical decomposition of the stratum corneum, in combination with topical application of TAC and 5-FU, is a safe, relatively painless, and efficient modality for the treatment of pediatric hypertrophic burn scars.

KEYWORDS

burn scars, fluorouracil, fractional skin ablation, hypertrophic, Percutaneous permeating, resurfacing, scar, Tixel, transdermal drug delivery, triamcinolone

1 | INTRODUCTION

Acute care of burn injuries has greatly improved in the last years; however, many patients develop hypertrophic scars that have permanent functional and social implications.[1,2] Hypertrophic scarring occurs when the normal healing process is disrupted by increased inflammation, and excess collagen accumulation, which can lead to an itchy, painful, erythematous, raised, and rigid scar.[2,3] The generally applied treatment for hypertrophic scars comprises of motion exercises, massage, pressure garments, steroid injections, silicone gel sheeting, laser and light-emitting diodes, cryotherapy, fluorouracil (5-FU), interferon, bleomycin, imiquimod 5% cream, and surgical interventions achieving only limited success, thus necessitating the development of newer, more effective treatment modalities.[4,6]

Burn scar treatment has important clinical and financial implications. For an example, in the United States alone, the cost of burn scar treatment has reached about $4 billion per year.[5]

Corticosteroid intralesional injections alone or combined with other modalities are the first-line treatment for hypertrophic scars and are considered the most efficacious.[7-11] Adverse events associated with corticosteroid intralesional injection include atrophy, hypo- or hyperpigmentation, telangiectasia, as well as severe pain during the injection, and laser-assisted corticosteroid drug delivery systems can ameliorate the depth and the amount of the drug which is been delivered.[12-18]

This study describes the safety and efficacy of thermal decomposition of the stratum corneum using a novel thermomechanical device to increase skin permeability for topical corticosteroid and 5FU application in the treatment of pediatric patients with hypertrophic scars.

2 | METHODS

This is a retrospective review of four patients (one male, three females) treated for hypertrophic burn scars between January 2015 and December 2017. Written consent was received from the legal guardians of the pediatric patients after they were informed of the nature of the procedure. Table 1 summarizes the patient demographics and clinical data.

The scars were treated by Tixel (NOVOXEL ltd). Device setting included 400°C at contact intervals of 5-8 ms, 1000 protrusion, and single pulse. Contact intervals were adjusted according to the patient's level of tolerance and comfort. Immediately after the Tixel treatment, triamcinolone acetonide (40 mg/mL) and 5-fluorouracil (50 mg/mL) mixed at a 1:9 ratio were topically applied to the treatment area at a dose of 1 cc per 1 cm^2. Sonophoresis was performed to enhance drug penetration using the impact device (Alma lasers GmbH, Germany, parameters: frequency 50 Hz, intensity 50%, 5 minutes) (Figure 1). Scars received eight treatments, 2-3 weeks apart.

Postprocedure care included topical trolamine (Biafine; Genmedix Ltd) self-applied 3-4 times per day for 3 days and the use of broad-spectrum sunscreen with a sun protection factor of 50 for 3 months.

The scars were evaluated using the Vancouver Scar Scale (VSS) by two independent dermatologists and photographed at baseline and 1-month postlast treatment. Pain level and satisfaction were assessed by the patient or his legal guardian by using the visual analog scale (VAS) and four-point scale (1-not satisfied, 2-mildly satisfied, 3-moderately satisfied, 4-highly satisfied), respectively. Scar toughness, thickness, color, and general aesthetic impression were rated on a four-point scale by the guardians as well (1-best, 4-worst).

Statistical analysis was performed using SPSS software (version 21.0; IBM Corporation).

3 | RESULTS

The study comprised of four patients: three girls 3, 4, and 4 years old, and 1 10-year old boy. All of which completed the study. There was a mean scar VSS reduction from 8.4 ± 0.8-5.2 ± 0.5 (*P*-value <.001) after eight treatments. Mean reduction of toughness, thickness, color, and general aesthetic impression were registered as follows: 3.1 ± 0.43 → 2.2 ± 0.31, 3.4 ± 0.5 → 1.9 ± 0.63, 2.7 ± 0.21 → 2.4 ± 0.25, and 3.23 ± 0.44 → 1.6 ± 0.64, respectively. Mean treatment pain VAS score was 1.74 ± 0.9. The patient's guardians rated their satisfaction level as "moderate-high." No severe adverse effects were noted.

4 | DISCUSSION

Hypertrophic scars are a common complication of wound healing process with a predilection to younger patients and higher Fitzpatrick

TABLE 1 Patient demographics and clinical data

Patient	Sex	Age	Fitzpatrick skin type	Disease Duration (Y's)	Anatomical location	VSSb-Average	VSSa-Average	VAS	Satisfaction	Vascularity before	Vascularity after
1	F	4	2	3	Chest	8	5.5	5.5	3	2.5	3
2	F	3	2	2	Abdomen	7.5	4.5	4.5	4	2	2
3	M	10	2	4	Shoulders	9.5	5.5	5.5	3	2.5	2.5
4	F	4	2	3	Abdomen	8.5	5.5	5.5	1	1.5	2
						8.375	5.25	5.25	2.75	2.125	2.375
						0.8	0.5	0.5	1.2	0.5	0.5

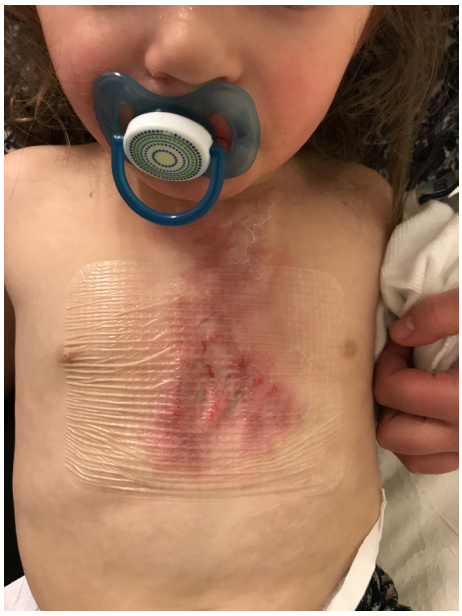

FIGURE 1 Patient # 1—Photograph immediately postfirst treatment

skin types, particularly patients of African, Asian, or Hispanic origin with an associated family history.[9] As topical steroid formulations demonstrate low poor cutaneous bioavailability, intralesional corticosteroid injections have been considered as first-line treatment mode for hypertrophic scars alone or in combination with other anti-scarring modalities such as intralesional injection of 5-fluorouracil, cryotherapy, surgical excision, radiation therapy, compression, and silicone-based dressings.[9,11] Potential adverse events associated with corticosteroid intralesional injection include dermal and fat atrophy, pigmentary alterations, and telangiectasia.[12] Severe pain during the multiple injection sessions is often a significant drawback, especially for children.[6,7]

Laser-assisted drug delivery of corticosteroid is considered a less painful treatment possibility and has demonstrated encouraging clinical results.[8,9] It provides efficient delivery of corticosteroids through the microscopic channels created by the ablative fractional laser.[9-11] Nevertheless, effective laser-assisted drug delivery is highly operator-dependent and painful enough. Lower energy might compromise penetration depth, whereas higher energy may cause coagulation, thus limiting drug delivery.[8-11]

The therapeutic efficacy of topical drugs relates both to their inherent potency and their ability to penetrate the different skin layers, with the primary permeation barrier being the stratum corneum. [19]

The Tixel system consists of a moving titanium tip heated to 400°C. The amount of thermal energy delivered to the skin is determined by the pulse duration and the protrusion. The pulse duration is the period of time that the tip is in contact with the skin, varying between 5 ms and 18 ms. The protrusion is defined as the distance in which the heated tip is moving measured from the edge of the handpiece distance gauge.

At low energy settings, the thermal effect on the viable epidermis and the dermis is limited. Most of the thermal effect is concentrated in the stratum corneum leading to rapid heat transfer and dehydration of the stratum corneum rather than coagulation. Desiccation leads to gentle elimination of the stratum corneum and establishes a concentration gradient by Fick's law; thus, enhancement of drug delivery following Tixel treatment is achieved.[20,21]

The impact device (Alma Lasers Ltd.) has been developed to enhance the delivery of topical cosmeceuticals. The device operates at low ultrasound frequency (~30 kHz-100 Hz) and energy of peak of 0.4 W/cm^2 effectively pushing topically applied liquids to enhance absorption when paired with the thermomechanical SC destruction produced by the Tixel.[22]

The primary outcome of the study was the significant reduction in the scars VSS score (*P*-value <.001). The secondary outcome was

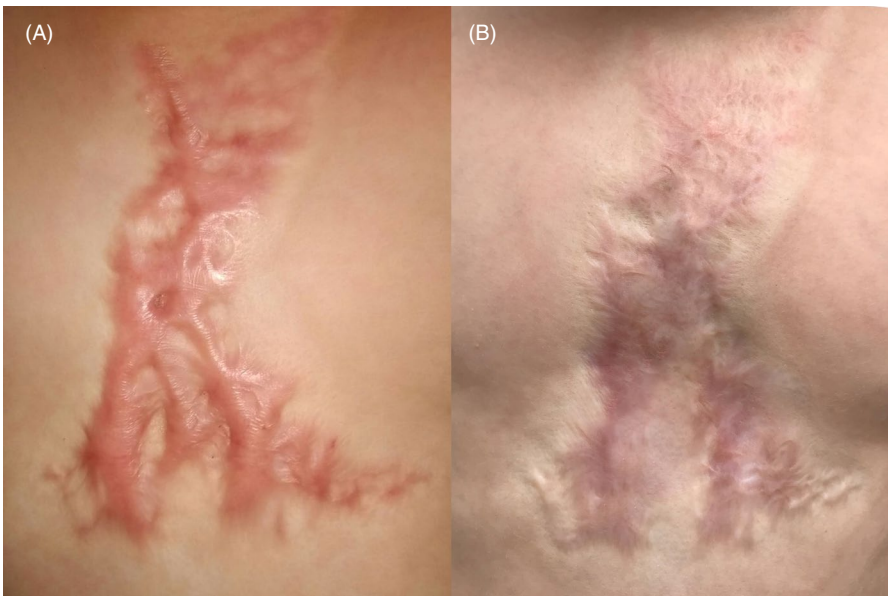

FIGURE 2 Patient # 1—Photographs of (A) baseline and (B) after completion of eight treatment protocol, 2 mo the last treatment

the consistently low pain reported during treatment with a mean VAS score of 1.74 (SD 0.9) (Figure 2).

This study demonstrates the successful and safe treatment of pediatric hypertrophic burn scars, thermal decomposition of the stratum corneum, followed by the immediate topical application of triamcinolone acetonide (TAC) with 5-fluorouracil (5FU). No significant adverse effects were reported with this approach. Moreover, the treatment was relatively painless and well tolerated in our patient group that refused alternative methods of treatment due to their previous painful experience. Even though our study was not explicitly aimed at achieving a uniform reduction of the scar, it is worthwhile noting that the scars seem to have been evenly reduced in height.

Additionally, the use of thermomechanical ablation as opposed to laser ablation eliminates the need for protective eyewear and could be performed by a nurse or medical assistant.

Limitations of this study include the small sample size and lack of a control group. Every new technology has a learning curve, and while results are significant and reproducible, further investigation is warranted to elucidate the best treatment protocol. The study raises several questions: What is the role of the Tixel in tissue remodeling? Is it only a drug delivery enhancing system? Does the heat transfer affect the dermal blood vessels? Might the thermal effect in itself lead to part of the improvement observed following treatment? Perhaps a combined treatment approach using both ablative and fractional laser therapy with Tixel may lead to superior results.

5 | CONCLUSION

Thermomechanical decomposition of the stratum corneum, in combination with topical application of TAC and 5-FU, is a safe relatively painless and efficient modality for the treatment of pediatric hypertrophic burn scars.

CONFLICT OF INTEREST

None.

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