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An enhanced transcutaneous delivery of botulinum toxin for the treatment of Hailey–Hailey disease

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Abstract

Successful treatment of Hailey–Hailey disease with intradermal botulinum toxin injections has been previously reported. The main disadvantages of this treatment are the excruciating pain and the risk of infections due to the numerous injections. We sought to evaluate the clinical effectiveness and safety profile of a novel approach using an energy-based device (Tixel, Novoxel, and Israel), followed by the topical application of botulinum toxin Type A for the treatment of Hailey–Hailey disease. A retrospective study of all cases of histologically diagnosed cases of Hailey-Hailey disease treated with Tixel device followed by topical application of botulinum toxin between 2018 and 2019 was performed. Epidemiologic, clinical, and treatment data, including effectiveness score and safety, were reviewed. The study included eight patients, of whom seven patients (87.5%) showed good or partial response. No systemic or local adverse effects were reported. There was no difference in effectivity between different body areas. Response to treatment ranged between patients with an average duration of 7.125 months after the second treatment. Tixel treatment followed by topical application of botulinum toxin can be considered in the treatment of Hailey–Hailey disease. This approach is less invasive, less painful, and yet effective as well as safe.

KEYWORDS

botulinum toxin, drug delivery, Hailey–Hailey disease

1 | INTRODUCTION

Hailey–Hailey disease or familial benign chronic pemphigus, first described in 1939 (Hailey & Hailey, 1939), is a rare chronic genetic blistering dermatosis, primarily involving the intertriginous areas, presenting with flaccid vesicles that can easily rapture, macerated fissured skin with chronic moist and vegetation (Burge, 1992), pain and malodor, significantly impairing patients' quality of life. The current treatment modalities comprise of corticosteroids, topical antimicrobials, oral antibiotics, laser ablation, photodynamic therapy, electron beam radiotherapy, dermabrasion, glycopyrrolate, afamelanotide, naltrexone, and botulinum toxin Type A (Campbell, McGrath, & Corry, 2018; Chiaravalloti & Payette, 2014; Farahnik et al., 2017; Kollman & Bass, 2018). Unfortunately, the disease is difficult to control and is recalcitrant to conventional therapies.

Treatment with botulinum toxin was first described in 2000 (Lapiere, Hirsh, Gordon, Cook, & Montalvo, 2000) with promising, several months lasting, results (Charlton, Stewart, & Rosen, 2018; Friedman, Koren, Niv, Mehrabi, & Artzi, 2019; Kothapalli & Caccetta, 2019). The main disadvantages of this treatment are the high cost of the toxin and the excruciating pain as well as the risk of infections due to the numerous needle punctures. Unfortunately, the skin barrier prevents the absorption of botulinum toxin while applied topically. Our case series study describes the clinical effectiveness and safety profile of a novel approach using an energy-based device (Tixel, Novoxel, and Israel) that thermally decomposes the stratum corneum,

followed by the topical application of botulinum toxin for the treatment for Hailey–Hailey disease.

2 | MATERIALS AND METHODS

This study was approved by an ethics committee and follows the tenets of the Declaration of Helsinki.

We performed a retrospective study of histologically diagnosed cases of Hailey–Hailey disease treated with Tixel device (parameters: exposure time 6–8 ms with 400–600 μm protrusion) followed by immediate topical application of botulinum toxin (125–250 units diluted with saline) and sonophoresis to enhance drug penetration using the Impact device (Alma lasers GmbH, Germany, parameters: Frequency 50 Hz, Intensity 50%, 5 min). This three steps treatment was preformed twice for each patient with 4–6 weeks intervals between the two treatments, bilaterally for the involved skin areas including axilla, groin, submammary and perianal areas. The patients were not treated with botulinum toxin 6 months prior to the treatment regimen. After each treatment, the patients applied topical cicalfate, and were instructed to avoid triggering factor including heat, sweating, and occlusive dressing. All patients signed a written consent form, after they were informed about the nature of the procedure and possible side effects. Epidemiological, clinical, treatment, and safety data were collected. Objective and subjective assessment was performed using the patient's global impression of change (PGIC) scale and the physician global assessment (PGA) scale. The treated area was photographed at baseline, before each treatment and 6–8 weeks after the two treatments. Two independent dermatologists retrospectively evaluated the patient's photographs. The PGA scale was graded on a scale of 0–7 with 0 being "no change or worsening" and 7 being "significant improvement." The PGIC was evaluated using a scale of 1–4, with 1 representing no remission, 2 representing partial remission, 3 representing nearly full, and 4 representing full remission. The last evaluating method used was the dermatology life quality index (DLQI). Histological changes of before (diagnostic biopsy) and 6–8 weeks following the two treatments were also evaluated in one patient.

3 | RESULTS

In total, eight patients (five males, three females; age range 32–57 years) with clinical presentation of Hailey–Hailey disease, confirmed histologically, were evaluated. The average disease duration was 16.875 years. The average weight and height were 70.5 and 170.2 respectively with the average body mass index (BMI) being 24.39. Patient's characteristics are shown in Table 1. Six patients received treatments for two body regions while the remaining two patients received the treatments for one involved area. The areas treated were axilla, groin, submammary, and perianal areas. Two (25%) patients achieved full remission, 4 (50%) showed a nearly full remission, one (12.5%) had a partial response and another one (12.5) did not response at all to the treatment. Thus seven patients (87.5%) had good or partial response to treatment. The baseline versus post-treatment representative clinical pictures of two patients and histology of one of the patients are shown in Figures 1 and 2, respectively. The average PGA scores 6–8 weeks after the final treatment were significantly improved compared with baseline. The average of the PGIC score was high with a mean of 5 in a scale of 0–7. The DLQI scores significantly improved with an average score of 22.75 before the treatments and an average score of 13.87, 6–8 weeks after the second treatment. Recurrence appeared up to 1 year with an average of 7.125 months after the second treatment. There was no difference in effectiveness between different body areas. Self-rated patients' satisfaction was high. No topical or systemic complications and

TABLE 1 Patients characteristics

#	Age	Sex	Weight	Height	FST	Family history	Disease duration	Areas involved	Past treatments
1	40	F	79	1,7	2	N	15	Axilla, groin, submamary, perianal	Topical: GBC
2	57	M	68	1,63	3	N	20	Groin, perianal	Topical: GBC, GPC, oral: Minocycline
3	59	M	69	1,8	2	Y	18	Axilla, groin, submamary, perianal	Topical: GBC, GPC, GBCC, oral: Minocycline
4	41	F	80	1,63	2	Y	25	Axilla, submamary	Topical: GBC
5	44	F	65	1,67	3	Y	12	Axilla, groin	Topical: Clobetasol propionate cream, betamethasone cream, tacrolimus ointment
6	32	M	66	1,78	3	N	15	Groin, perianal	Topical: GBC,GPC, GBCC, oral: Minocycline
7	45	M	78	1,69	3	Y	11	Axilla, groin, submamary	Topical: GBC, tacrolimus ointment, oral: Minocycline
8	37	M	59	1,72	2	Y	19	Axilla, submamary	Topical: GBC,GPC, oral: Minocycline
Average	44.375	–	70,5	170,2	2.5	–	16.875	–	–

Abbreviations: FST, fitzpatric skin type; GBC, gentamicin-betamethasone cream; GPC, gentamicin-prednisolone cream; GBCC, gentamicin-betamethasone-clotrimazole cream.

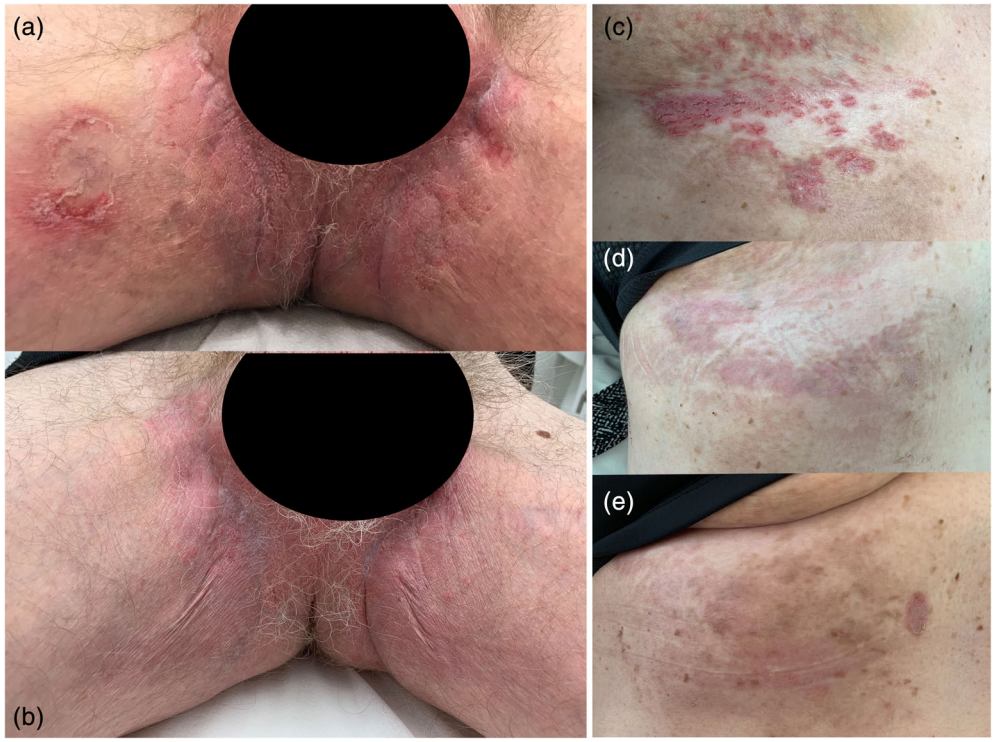

FIGURE 1 Representative before (a,c) and 1 month after (b,d) treatment photographs. Photograph "e" was taken 7 months post-last treatment

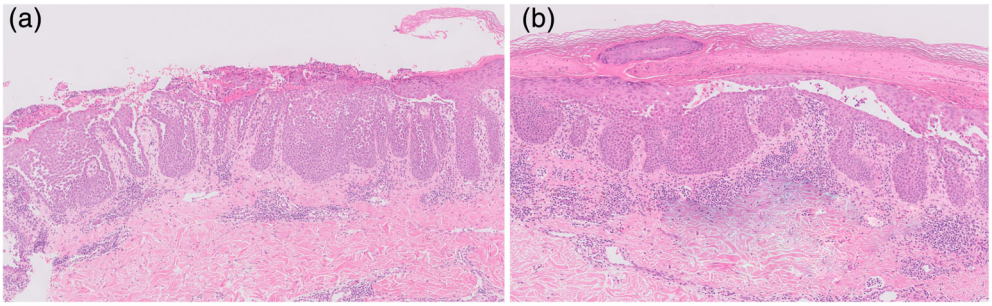

FIGURE 2 Histological comparison of before (a) and after (b) treatment. (a) Before: Skin showing intraepidermal acantholysis involving all the epidermal layers with surface erosion and a mild superficial perivascular lymphocytic infiltrate with scattered eosinophils. (b) After: Skin biopsy showing intraepidermal acantholysis in the mid stratum spinosum with regeneration of stratum spinosum, basal, and granular layers. Hyperkeratosis in basket wave pattern, subcorneal fibrin with scattered neutrophils, and parakeratotic cells. A denser (compared with baseline) superficial perivascular lymphocytic infiltrate present with numerous eosinophils

adverse effects were reported. Treatment characteristics and results are summarized in Tables 2 and 3, respectively.

4 | DISCUSSION

Hailey–Hailey disease is a chronic noncurable disease. Many treatment modalities were suggested in the past, however the disease is still recalcitrant to conventional therapy and significantly damage the quality of life of all patients. Since botulinum toxin decreases sweat production it is used for the treatment of hyperhidrosis (de Almeida & Montagner, 2014; Glaser & Galperin, 2014). This effect and the subsequent decrease of microorganism colonization might serve as one explanation for its efficacy in the treatment of Hailey–Hailey disease (Benohanian, 2005). Botulinum toxin cannot cross the stratum corneum, therefore, its injection is required for both the treatment of hyperhidrosis (de Almeida & Montagner, 2014; Glaser & Galperin, 2014) and for the treatment of Hailey–Hailey disease (Charlton et al., 2018; Friedman et al., 2019; Kothapalli & Caccetta, 2019; Lapiere et al., 2000). It is an effective treatment but a painful, expensive, and the duration effects is for several months only.

This led us to try a novel approach of enhanced transcutaneous delivery. Tixel is a novel nonlaser thermo-mechanical system (Tixel, Novoxel, and Israel), that is, a registered medical device in several countries worldwide. The mechanism of action is by evaporation and thermal decomposition of stratum corneum and the dehydration of epidermis (Elman, Fournier, Barneon, Bernstein, & Lask, 2015). These effects allow the penetration of topically applied Botulinum toxin into

TABLE 2 Treatments characteristics

#	No of treated areas	Treated area	Number of treatments	Tixel parameters	Dysport U/unit-1	Dysport U/unit-2	Dilution
1	2	Axilla, groin	2	6–8/400–500	250	125	500/6
2	2	Groin, perianal	2	6–8/400–501	250	250	500/6
3	2	Groin, submamary	2	6–8/400–502	250	250	500/6
4	2	Axilla, submamary	2	6–8/400–503	250	125	500/6
5	1	Axilla	2	6–8/400–504	250	250	500/6
6	1	Groin	2	6–8/400–505	250	250	500/6
7	2	Axilla, submamary	2	6–8/400–506	250	250	500/6
8	2	Axilla, submamary	2	6–8/400–507	250	125	500/6

TABLE 3 Results

#	PGICS	DLQI-base	DLQI-1.5 month	Delta-DLQI	PGA1	PGA2	PGA-Ave	VAS	Satisfaction	Remission (months)	Duration (months)
1	5	23	14	9	1	1	1	2	3	3	10
2	6	21	11	10	2	2	2	3	4	3	6
3	5	24	19	5	1	1	1	2	2	2	6
4	5	22	12	10	2	1	2	2	3	3	6
5	6	18	11	7	1	1	1	3	3	3	4
6	5	23	9	14	1	2	2	3	3	4	12
7	3	25	22	3	3	3	3	2	1	1	2
8	5	26	13	13	2	1	2	3	3	4	11
Average	5	2,275	13,875	8,875	1,625	1,5	1.75	2,5	2.75	2.875	7.125

Abbreviations: DLQI, dermatology life quality index; PGA, physician global assessment; PGA-Ave, physician global assessment average; PGICS, patient's global impression of change scale; VAS, visual analogue scale.

the skin through the stratum corneum. This system has already been demonstrated to significantly increase the permeability of a couple of topically applied medications including, lidocaine (Sintov & Brandys-Sitton, 2006) and as proved by Friedman et al. also Botulinium toxin (which was used in severe cases of rosacea; Friedman et al., 2019).

Our case series shows promising results with high satisfaction rate, high degree of symptoms resolution, lasting effect of up to 1 year (with an average duration of 7 months), and without any topical or systemic side effect. Out of the eight patients, one patient did not respond as well as the others. It was not clear what was the reason for the treatment failure. This 45 years old male patient received treatments for two body area: the axilla and the submammary area, as did other patients who responded well to the treatment. He had a BMI of 27.4 (a bit higher than the average), and disease duration was 11 years (less than the 16.7 years average).

The limitations of this case series are its nature—an uncontrolled retrospective study with a small study group and no control for comparison. Additional double blind, placebo controlled, comparative prospective studied with bigger cohorts, are required in order to strengthen our observation of the efficiency of enhanced transcutaneous botulinum toxin delivery for Hailey–Hailey disease.

In conclusion, Tixel treatment followed by the topical application of botulinum toxin showed good results in the treatment of Hailey–Hailey disease. This safe approach is an effective, long lasting, less invasive, and less painful additional tool in treating patients with Hailey–Hailey disease.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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