

Treatment of Epidermolysis Bullosa Simplex, Weber-Cockayne Type, With Botulinum Toxin Type A

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 43-year-old white woman with a history of epidermolysis bullosa simplex (EBS), Weber-Cockayne type (EBS-WC), which she had had since childhood, presented with multiple blisters, erosions, and crusts on the bottom of both feet (**Figure 1**). During most of her life, new blisters would arise and then heal after several weeks. Severe flares would occur during the summer months and on vacations to warm climates. Previous treatments included aluminum chloride and tetracycline. The patient's mother, sister, and son also had a history of EBS-WC. Her medical history was otherwise unremarkable. The only medication she was taking was an oral contraceptive pill, and she reported a drug allergy to penicillin.

Physical examination revealed a total of 17 blisters and erosions measuring 0.5 to 3.0 cm on the plantar aspect of the feet. The hands and the rest of the skin were clear. A lesion had previously been biopsied, and the findings confirmed a diagnosis of EBS-WC.

THERAPEUTIC CHALLENGE

Current treatment options for EBS have been difficult. Mechanical protection of the traumatized area can help prevent blisters, but such protection is often difficult during summer months. Anecdotal reports of the application of aluminum chloride have showed promise owing to its antiperspirant properties.^{1,2} Younger et al³ conducted a double-blind, placebo-controlled crossover study of topical aluminum chloride, 20%, in 23 subjects with EBS-WC, which failed to show any difference between the treated and placebo groups. Other topical therapies include high-potency corticosteroids, antibiotics,⁴ and nonsteroidal anti-inflammatory agents such as bufexamac.⁵ There have been anecdotal reports of success with the use of tetracycline,^{6,7} although a double-blind, placebo-controlled, randomized study failed to show any difference between antibiotic therapy and treatment with placebo.⁸ Other systemic therapies for EBS have included cyproheptadine,^{9,10} corticosteroids, and retinoids.

Recently, there have been reports on the treatment of palmer and plantar hyperhidrosis with botulinum toxin type A (BTX-A) (Botox; Allergan Inc, Irvine, California), which has been shown to be simple, safe, and effective.^{11,12} Because hyperhidrosis leads to frictional trauma and the development of blisters in EBS, it was thought that BTX-A could have a therapeutic role in this condition.

SOLUTION

One foot of our patient was treated with BTX-A injections, and the other (control) foot received injections of isotonic sodium chloride (normal saline) solution. First, a Minor iodine-starch test was performed to reveal the



Figure 1. Patient's feet before treatment.

areas of high sweating. Then, analgesia of the soles was achieved by blocking the posterior tibial nerve and the sural nerve.¹³ Lidocaine (4 mL), 2%, was injected posterior to the pulse of the tibial artery and between the Achilles tendon and the superior border of the lateral malleolus. One bottle of BTX-A was diluted with 10 mL of preserved sterile saline (1 U/0.1 mL); then, 0.1 mL of BTX-A was injected into the middle to deep dermis on the plantar aspect of the right foot at 1-cm intervals. A total of 100 U were used. The lateral aspect of the foot and the area between the toes were not treated. The approximate area of the right foot that received the BTX-A injections was 166.5 cm². The left foot, which served as a control, only received injections of preserved sterile saline, without any toxin. The investigators were blinded and did not know which foot had received the BTX-A during the entire length of the study. The study was approved by the institutional review board committee at Roger Williams Hospital, Providence, Rhode Island. The patient signed a consent form, as well as a photography release form, before the treatment visit. The BTX-A was

provided by the Department of Dermatology at Roger Williams Medical Center.

The patient was followed up for 3 months. She tolerated the procedure extremely well and did not experience any adverse events from the injections. She did not develop any bruising, hematomas, or increase in blisters. After 2 weeks, she reported a decrease in pain and perspiration on the right foot, which had received the BTX-A. Also, she noted a decrease in blister formation on the BTX-A-treated foot. All blisters were traced, and then the area was calculated with a digital wound measurement device (Visitrak; Smith & Nephew, Largo, Florida). The foot that received the BTX-A injections had fewer blisters than the control foot. The mean area of blister formation after therapy was 3.57 cm² in the treated foot and 5.41 cm² in the control foot. These values represented a 34% difference between the treated and the nontreated feet. The mean number of blisters was 6.57 in the foot treated with BTX-A and 8.42 in the control foot. Before treatment, the foot that would receive the BTX-A had 11 blisters and a total blister area of 4.6 cm², while the control foot had 6 blisters and a total blister area of 2.6 cm². Three weeks after treatment, a therapeutic benefit was already noticeable in the treated foot. In the control foot, however, newly formed blisters were still evident (**Figure 2**). At the end of 3 months, the BTX-A-treated foot had 4 blisters, with a total blister area of 1.6 cm², while the control foot had 9 blisters, with a total blister area of 2.4 cm². These values represented a 64% decrease in the number of blisters and a 65% reduction in blister surface area in the treated foot (**Table**). Most of the blisters that did develop in the BTX-A-treated foot occurred on the lateral edges and between the toes, not on the plantar aspect. This represented areas of the foot that did not receive the BTX-A injections.



Figure 2. Patient's left foot 3 weeks after treatment with isotonic sodium chloride injections (A) and her right foot after botulinum toxin type A injections (B).

COMMENT

Inherited epidermolysis bullosa comprises a group of rare genetic disorders that are characterized by the development of blisters after minor trauma to the skin. There are 3 major categories: simplex, junctional, and dystrophic. There are more than 25 known forms within these categories and more than 10 different gene mutations for proteins that normally reside in the epidermis, dermoepidermal junction, and superficial papillary dermis.

Epidermolysis bullosa simplex is usually inherited in an autosomal dominant manner and results from the genetic mutation of keratins 5 and 14, which are interme-

Table. Blister Data Before and After Treatment With Botulinum Toxin Type A

Foot	Before Treatment		After Treatment				
	No. of Blisters	Surface Area, cm ²	No. of Blisters	Surface Area, cm ²	Difference in No. of Blisters, %	Difference in Blister Surface Area, %	Mean Blister Surface Area, cm ²
Right	11	4.6	4	1.6	64 (↓)	65 (↓)	3.57
Left	6	2.6	9	2.4	50 (↑)	8 (↓)	5.41

diate filaments that are normally present in the basal layer of the epidermis.¹⁴ This mutation in turn produces a weakness in keratinocyte adhesion and subsequently leads to blister formation within the lower part of the epidermis. Epidermolysis bullosa simplex can be further divided into the following subtypes: localized, or EBS-WC; generalized, or Koebner EBS; herpetiform, or Dowling-Meara EBS; EBS with mottled pigmentation; and EBS with muscular dystrophy.¹⁵

A recurrent blistering eruption of the hands and feet after frictional trauma is characteristic of EBS-WC. Exacerbations and increased blister formation occur during hot weather, prolonged walking, or physical activity. Hyperhidrosis is a common associated finding. The increase in blister development that occurs during hot summer months is thought to be attributable to an increase in the coefficient of friction of the skin caused by sweating and raised skin temperature.¹⁶ The Weber-Cockayne type of EBS is caused by a genetic mutation in the keratin intermediate filaments 5 and 14 in the basal layer of the epidermis. Increased mechanical stress, which often occurs when hyperhidrosis is present, then leads to blister formation.

Historically, EBS has been difficult to treat. Treatment has been aimed at preventing blister formation with appropriate wound dressings, preventing inflammation and bacterial superinfection with oral antibiotics, and decreasing sweating with aluminum chloride therapy.

The present case illustrates that BTX-A may play a role in the treatment of EBS-WC. The mechanism of action of BTX-A involves blockage of the cholinergic nerve terminals and inhibition of the release of acetylcholine. As well as acting at the neuromuscular junction, BTX-A also blocks the autonomic cholinergic junctions of the postganglionic sympathetic fibers to the sweat glands, making it an ideal therapy for hyperhidrosis. There have been a few reported adverse effects after local injections of BTX-A, including weakness in the muscles adjacent to the treatment sites. Beneficial results last for 4 months but may continue for up to 1 year.

This article presents only 1 case of BTX-A-treated EBS-WC, but the results look promising. Although a 64% reduction in blister count appears clinically significant, larger case-controlled, double-blinded studies are needed to further elucidate these results. Also, using a higher concentration of BTX-A, such as 2 U/0.1 mL, for a total of 150 to 200 U per foot, may be more effective. Furthermore, treatment should not be limited to the plantar aspect of the foot, it should also involve the lateral surface and the area between the toes. We hope that this case report stimulates the production of further studies of this nature.

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