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ORIGINAL ARTICLE
Botulinum toxin A for the management of vulvodynia

H Yoon, WS Chung and BS Shim

Department of Urology, Ewha Womans University, Mokdong Hospital, Seoul, Republic of Korea

Clinically, botulinum toxin A blocks the cholinergic innervation of the target tissue. Recently, it has been proved effective not only at a neuromuscular junction but also within parasympathetic or sympathetic neural synapses. Seven women with pain on genitalia that could not be controlled with conventional pain managements were enrolled in this study. Twenty to 40 U of botulinum toxin A were used in each injection. Injection sites were the vestibule, levator ani muscle or the perineal body. Repeat injections were administered every 2 weeks if the patient's symptoms had not fully subsided. In all patients, pain had disappeared with botulinum toxin A injections. Five patients needed to be injected twice; the other two patients needed only one injection. We did not observe complications related to botulinum toxin A injections, such as pain, hemorrhage, infection, muscle paralysis or other complications. The subjective pain score improved from 8.3 to 1.4, and no one has experienced a recurrence (the follow-up period was four to 24 months, with a mean follow-up of 11.6 months). Botulinum toxin A is effective in blocking nociception. Even though further investigation and well-controlled study will be necessary, we suggest that the botulinum toxin therapy would be useful and safe in managing vulvodynia of muscular or neuroinflammatory origins.
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Introduction

Vulvodynia often causes sexual dysfunction, which is not only pain but arousal or orgasmic difficulty as well. However, its etiology is not yet clearly defined. Therefore, treatments of vulvodynia are mainly symptomatic, and pharmacologic, relying on anti-inflammatories, and analgesics. Even though biofeedback, physical therapy, psychological support and surgical excision of lesion sites are used to improve painful symptoms, no one treatment has been proved to be most effective or ideal.

Pain in the genitalia often leads to avoiding sexual contact due to fear of pain. Predicted pain also leads to difficulty in arousal and orgasm. Therefore, when we consider vulvodynia management, we also consider proper arousal and saving of orgasmic capacity as well. Pain killers, antidepressants or local anesthetics have been used to manage the pain, but some of these agents have systemic or sexual side effects.

Recently, botulinum toxin, which has been used to paralyze muscle, has begun to be used for various types of pain without significant side effects. Sexual pain disorder, such as vulvar pain syndrome or vulvodynia, is one of its newly developed indications.[1–5]

In this study, we will report our early experience on the study of the effects of botulinum toxin A on the management of vulvodynia.

Materials and methods

Seven women with intractable genital pain (coital and/or noncoital pain) were given botulinum toxin A (Botox, Allegran, USA) injections. Past and current medical histories were taken, and physical examinations were performed on all patients to insure localization and characteristics of pain. All of their histories included various medical trials to treat genital pain but without significant improvement. Because they had failed to respond to multiple forms of therapy, they were offered botulinum toxin A injections. Only after obtaining their informed consent were the toxin injections given.

Correspondence: Dr H Yoon, Department of Urology, Ewha Womans University, Mokdong Hospital, #911-Mokdong, Yangcheon-ku, Seoul 158-710, Republic of Korea.
E-mail: wowhana@ewha.ac.kr
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Pain questionnaires, which included information regarding pain site, duration, characteristics and visual analog scale, were completed by the patients before and 2 weeks after each injection. Patients were told to report dizziness, nausea, breathing difficulties, chest tightness or palpitations after the injections.

All procedures were performed at an outpatient clinic. Before starting the injection procedure, the exact pain sites were confirmed with light touching by a cotton tip and gentle digital palpation. The injections were then administered at the pain sites (Figure 1), with 20 U of the botulinum toxin diluted using isotonic saline. The amount of each injection was 0.2–0.3 cm^3. If the site to be injected covered a wide area, the injections were evenly distributed, 1 cm apart. Up to 20 U of botulinum toxin A were injected at each pain site. Injection sites were the vestibule (4), levator ani muscle (2) and the perineal body (1). Prophylactic oral antibiotics were given for 3 days starting on the day of injection. The pain level was re-evaluated 2 weeks after the injections. If the patient still had significant pain, we repeated the injections increasing the dosage (to 40 U) at every pain site.

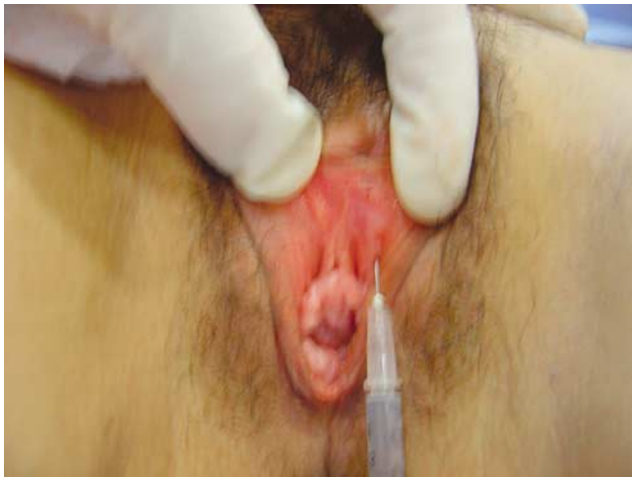

Figure 1 Injection of Botulinum toxin A at the pain site of the vestibule.

Results

Physical examinations confirmed that none of the patients had gross abnormalities or significant lesions, only intractable pain that interrupted their sexual activities (Table 1). Digital examination revealed that two of the seven women had elevated tone in the levator ani muscle, which was suspected to be the cause of their pain. However, they did not have any experience of vaginismus, but pain in the genitalia. Five women had normal or decreased levator muscle tone, which was not painful on digital palpation, but they did feel pain on the vestibule (4) or the perineal body (1).

In all seven patients, pain decreased or disappeared after botulinum toxin A injections. In two cases, pain decreased with only one injection. One of them had persistent pain on her perineal body after a perineorrhaphy 6 months ago. Another had pain on the vestibule. The other five cases needed injections twice to reach a satisfactory level of pain relief. The mean visual analog pain score was 1.4 after the botulinum toxin A injection treatment; it had been 8.3 before the treatment (Table 2). We did not observe significant bleeding, infection, muscle paralysis, voiding difficulty, bowel problems or other botulinum toxin-related complications, such as nausea or flu-like symptoms.

The patients reported that, after the treatment, they experienced subjective improvement in their sexual life, having no significant pain or discomfort during or after intercourse. However, we did not evaluate changes in arousal or orgasmic intensity for each patient relating botulinum toxin A injections.

Discussion

Vulvodynia, vulvar vestibulitis or vulvar pain syndrome is complex, often with resulting dyspar-

Table 1 Characteristics of the patients

No	*Age/sex*	*Status of menopause*	*HRT*	*Previous Tx.*	*Duration of pain*
1	28/F	Premenopause	—	Analgesics, antibiotics	1 year
2	38/F	Premenopause	—	Analgesics, NSAID	6 months
3	59/F	Postmenopause	E + P[a]	Analgesics, antibiotics	3 years
4	61/F	Postmenopause	E[b]	Analgesics, NSAID	1 years
5	45/F	Premenopause	—	Analgesics, NSAID, antibiotics 2 months	
6	36/F	Premenopause	—	Analgesics, NSAID	8 months
7	34/F	Premenopause	—	Analgesics, NSAID	8 months

[a]E + P, HRT with conjugated estrogen and progesterone.
[b]E, HRT with conjugated estrogen.

Table 2 Injection sites and doses in each patient

No.	*Site of injection*	*Does of injection (1st/2nd, U)*	*Pain score (VAS[a]) pre/post*
1	Levator ani m.	20/40	10/2
2	Vestibule	20/40	8/1
3	Vestibule	20/40	7/0
4	Vestibule	20	9/0
5	Perineal body	20	10/0
6	Levator ani m.	20/40	7/1
7	Vestibule	20/40	8/2

[a]VAS ; visual analog scale.

eunia, but its exact etiology remains unclear. Aberrant nociception, it is believed, has a primary role in vulvodynia with both peripheral and central mechanisms implicated.[6] A localized pain in the vestibule without gross infection is thought to result from an intraepithelial neural hyperplasia and peripheral nociceptor sensitization.[7–9] Therefore, it is difficult to determine whether pelvic floor dysfunction, such as hypertonicity, is a secondary phenomenon, resulting from vulvar vestibulitis or an independent symptom. In our study, two patients with levator ani muscle spasm did not show vestibular pain during intercourse, but positive findings after physical examination, including a cotton tip test, lead us to suspect vulvar vestibulitis. However, in this instance, we injected the botulinum toxin into the painful site on the levator muscle, not on the vestibule, and the results were satisfactory.

Botulinum toxin is a neurotoxin produced by the Gram-positive anaerobic organism, *Clostridium botulium*. It is one of the most poisonous natural toxins.[10] The neurotoxin binds to the synaptic cholinergic terminals of a neuromuscular junction and inhibits acetylcholine release. The affected nerve terminals do not degenerate, and function recovers through axonal sprouting and the formation of new synaptic contacts.[11] The time necessary to recover function from paralysis depends on toxin type and the type of nerve terminals. It usually takes 2–4 months at the mammalian N–M junction, and longer in autonomic neurons, sometimes more than a year.[12] Autonomic effects are based on the toxin's blocking effect with respect to acetylcholine release in all parasympathetic and post-ganglionic sympathetic neurons.

Aside from its transient chemodenervation of skeletal or smooth muscle, a peripheral antinociceptive effect from botulinum toxin A has been suggested. There are several reports of its antinociceptive effects on various diseases, such as interstitial cystitis, genital pain, chronic pelvic pain and chronic myofascial pain syndrome.[5] In addition, Jabbari *et al*.[13] reported a sustained analgesic effect related to allodynia and burning pain after subcutaneous injection of botulinum toxin A in two spinal cord abnormalities. This report shows that botulinum toxin A has a clinical effect in the control of nociception.

The effect of botulinum toxin A injection on dyspareunia can be explained in two ways. One way is decreasing pain by decreasing the abnormal hypertonicity of the pelvic floor through the toxin's muscle paralysis effect. Involuntary tonic contraction of the pelvic floor muscle can be a defensive reaction, one that is triggered by vulvar pain. At that point, dyspareunia may be aggravated. Paralyzing this muscle can lessen the pain, which is worsened by muscle spasms.

Another mechanism blocks neurotransmission at the nociceptive receptors, which are distributed in the submucosal layers of the vestibule. This kind of mechanism can be applied to the botulinum toxin injection treatment of interstitial cystitis.[5]

There are a few reports on the ability of botulinum toxin A to manage vulvodynia or vulvar pain syndrome, but the results are promising. Injection of botulinum toxin A brought about a marked improvement in patients with intractable pain, which was not controlled with various conventional management programs.[3–5] It is thought that during conditions of chronic inflammation and pain, efferent functions of the sensory nerves play a prominent role in sensitizing afferent nerve terminals to peripheral stimuli. In particular, as seen in this study, in vulvodynia treatment without pelvic floor muscle spasm, the effect of botulinum toxin A may be based on the neuronal uptake of the toxin or its metabolites, with subsequent effects on peripheral and/or central nociceptors.[1–3] In addition, botulinum toxin A induced alterations in the neurosecretion of neurotransmitters, and neuropeptides may participate in lessening the pain.[3]

At this time, it is unclear how the pain-controlling mechanism of botulinum toxin A works, especially in case of chronic pain from chronic inflammation. However, mounting data reveal the excellent antinociceptive effect of botulinum toxin A without significant side effects. Therefore, botulinum toxin A can be applied to chronic pain of unknown etiology, such as vulvodynia and chronic pelvic pain.

In this study, we observed positive results in managing dyspareunia with botulinum toxin A. Although the effect of further treatment, including long-term effects and pathophysiologic changes, should be investigated, botulinum toxin A appears to be a promising option for managing sexual pain disorder.

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