

# Botulinum Toxin Type A for the Treatment of Provoked Vestibulodynia

## An Open-Label, Pilot Study

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**OBJECTIVE:** To evaluate the effects of botulinum toxin type A for the treatment of provoked vestibulodynia.

**STUDY DESIGN:** Open-label, dose-escalation, pilot study. Primary outcome measure was a standard numeric pain rating scale of 0–10. Secondary measures were improvements in quality of life and change in medication use.

**RESULTS:** The 7 patients who received 35 units of botulinum toxin type A had a baseline mean pain score (0–10) of 8.1 (SD = 0.70). Thirty days after treatment, these patients had a mean pain score of 2.9 (SD = 1.17). The duration of effect was 8 weeks, and there were no side effects. The 12 patients who received 50 units of botulinum toxin type A had a baseline mean pain score of 7.4 (SD = 0.10). Thirty days after treatment, these patients had a mean pain score of 1.8 (SD = 0.72). The duration of effect was 14 weeks, and there were no side effects. Significant improvement was also seen in medication use and quality of life for these patients.

**CONCLUSION:** This study provides further clinical evidence of the nociceptive effects of botulinum toxin type A in pelvic inflammatory pain-related disorders. Double-blind, placebo-controlled trials to evaluate the efficacy of botulinum toxin in treating patients with provoked

vestibulodynia are warranted. (J Reprod Med 2006; 51:467–470)

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**All patients had relief of their symptoms following BoNT/A injections.**

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**Keywords:** botulinum A toxin, vulvar diseases, pelvic pain, provoked vestibulodynia.

*Vulvodynia* refers to vulvar pain occurring in the absence of an underlying, recognizable disease. It can be generalized or localized and can occur spontaneously or from physical provocation.<sup>1</sup> It is estimated that 14 million women in the United States may have vulvodynia at some point in their lives.<sup>2,3</sup> The onset of vulvodynia is usually abrupt, and the typical patient is between the ages of 20 and 45 years. Patients describe their symptoms as vaginal soreness, burning, dryness, rawness, deep irritation and pressure. Intercourse and speculum examinations are always painful. Direct digital palpation of the pelvic floor muscles may elicit a painful spasm. Tight clothing, exercise, and prolonged sitting or walking may exacerbate the symptoms. Duration of symptoms varies from 6 months to >2 years.

The pain mechanism implicated in vulvodynia may involve central nervous system dysfunction

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Supported by a research grant from Allergan Pharmaceuticals, Inc., Irvine, California, for the purchase of botulinum toxin type A used in this study.

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**Financial Disclosure:** The authors have no connection to any companies or products mentioned in this article.

and/or activation of nociceptors leading to peripheral sensitization, with an increased number of nociceptors in the vestibular mucosa.<sup>4-6</sup>

Effective therapy does not exist for many of these patients. Current treatment includes biofeedback, cold, oral medications such as tricyclic antidepressants, topical ointments with anesthetics, injections with steroids and surgery to excise the involved vulvar tissue.<sup>7-9</sup>

There are limited reports of the use of botulinum toxin type A (BoNT/A) in the treatment of vaginismus.<sup>10-12</sup> These studies used a dose range of 10–100 units (Botox, Allergan Inc., Irvine, California) or 150–400 units (Dysport, Ipsen Biopharm Ltd., Bath, U.K.) and had an efficacy (duration) of 1–2.5 months (Botox) and 12.5 months (Dysport). Additionally, these studies vary in method, injection site, number of injections, dilution and use of electromyography (EMG).

We performed an open-label, dose-escalation, pilot study to further test the efficacy of BoNT/A to relieve vulvar pain classified as provoked vestibulodynia (formerly vestibulitis).

### Methods

Patients were recruited from the Minnesota Gynecology and Surgery Clinic. All patients with a history of vulvodynia were eligible for the study. Those patients who demonstrated provoked vestibulodynia by history and examination were treated. All patients with symptoms for > 6 months, severe pain on vestibular touch or attempted vaginal entry, tenderness to pressure localized within the vulvar vestibule, age of 18 years or older, body weight of at least 45.36 kg and a clinical examination acceptable to the investigator were eligible for the study. The first 7 patients who met the criteria for the study and signed the informed consent form were enrolled.

Three to 4 painful vulvar areas in 7 patients were identified by touch with a cotton swab. Thirty-five units of BoNT/A (Botox) in 0.35 mL unpreserved normal saline were divided equally and injected into the painful areas. Injections were made using a tuberculin syringe and a 30-gauge, 4.40-mm needle into muscle/soft tissue without EMG guidance or local anesthesia. There was no attempt to inject specific muscles; rather, the toxin was allowed to disperse below the vestibular epithelium in the identified painful areas. Follow-up was at 30 days and 12 weeks or when the pain returned to baseline. The primary outcome measure was a standard numeric

pain rating scale of 0–10. Secondary outcome measures were improvements in quality of life, decrease in pain and change in medication use. The mean age of the patients was 36 years (range, 51–73).

A second group of 12 patients (7 from the first group and 5 new patients) were injected with 50 units of BoNT/A, as with the first group. The 7 patients from the first group were not reinjected before 3 months and until they had reached baseline. Follow up time and outcome measures were the same. The mean age of the patients was 34 years (range, 51–23).

### Results

The 7 patients who received 35 units of BoNT/A had a baseline mean pain score of 8.1 (SD=0.70). Thirty days after treatment, these patients had a mean pain score of 2.9 (SD=1.17) (Table I). A paired *t* test of the pre/post pain score difference indicated that these 7 patients experienced an average pain score decrease of 5.3 (SE = 0.36, *p* < 0.0001) after treatment with BoNT/A. The duration of effect (when the patient called for reinjection) in these 7 patients lasted 8 weeks, and there were no side effects.

The 12 patients who received 50 units of BoNT/A had a baseline mean pain score of 7.4 (SD=0.10). Thirty days after treatment, these patients had a mean pain score of 1.8 (SD=0.72) (Table II). A paired *t* test of the pre/post pain score difference indicated that these 12 patients experienced an average pain score decrease of 5.6 (SE = 0.19, *p* = 0.0001) after treatment with BoNT/A. The duration of effect (when the patient called for reinjection) in these 12 patients lasted 14 weeks, and there were no side effects.

**Table I** Injection of 35 Units of BoNT/A

Patient no.	Age (yr)	BL	30d	Difference
1	51	9.0	4.0	5.0
2	33	8.0	4.0	4.0
3	40	9.0	3.0	6.0
4	23	8.0	3.0	5.0
5	38	8.0	1.0	7.0
6	37	7.0	2.0	5.0
7	32	8.0	3.0	5.0
Mean	36	8.1	2.9	5.3

Summary and means of age, BoNT/A baseline (BL) pain score, pain score at 30 days (30d) after BoNT/A injection and pain score difference between BL and 30d. This initial series consisted of 7 patients and 35 units of BoNT/A.

**Table II** Injection of 50 Units of BoNT/A

Patient no.	Age (yr)	BL	30d	Difference
1	51	8.0	2.0	6.0
2	33	6.0	1.0	5.0
3	40	8.0	2.0	6.0
4	23	8.0	2.0	6.0
5	38	6.0	1.0	5.0
6	37	6.0	2.0	4.0
7	32	7.0	1.0	6.0
8	32	8.0	3.0	5.0
9	29	7.0	1.0	6.0
10	31	8.0	2.0	6.0
11	36	9.0	3.0	6.0
12	28	8.0	2.0	6.0
Mean	34	7.4	1.8	5.6

Summary and means of age, pre-BoNT/A baseline (BL) pain score, pain score at 30 days (30d) after BoNT/A injection and pain score difference between BL and 30d. This second series consisted of 12 patients and 50 Units of BoNT/A.

All patients were able to decrease their oral pain medications. Significant improvement was also seen in the quality of life for 3 patients who were able to have pain-free intercourse for the first time in several years. Six patients noted decreased pain on intercourse, and 3 patients (who were not sexually active) noted a marked decrease in pain on palpation.

### Discussion

Botulinum toxin has been used to treat movement disorders, spasticity, glandular hyperactivity and cosmetic lines. There are 3 commercially available preparations of botulinum toxin: Botox and Dysport are type-A neurotoxins, and Myobloc (Solstice Neurosciences Inc., San Francisco, California) is a type-B neurotoxin. These botulinum toxins are produced from different strains of the bacterium *Clostridium botulinum*. All these toxins differ in potency and dose, and therefore their units are not interchangeable.<sup>13</sup>

The toxins affect release of neurotransmitters by cleaving specific proteins (SNAP-25 for toxin type A and VAMP for toxin type B) responsible for docking and fusion of the acetylcholine vesicle to the presynaptic membrane.<sup>14</sup> This in turn interferes with the process of neurotransmitter release, resulting in muscle relaxation.

Recently BoNT/A was also used to treat such painful conditions as headache, torticollis and myofascial pain.<sup>15-18</sup> The effect of BoNT/A on pain is thought to be from its inhibitory release of neuropeptides involved in pain and inflammation

along with its inhibition of muscle spasticity.<sup>19</sup>

In vitro cell culture studies have demonstrated that BoNT/A inhibits capsaicin-stimulated release of substance P from embryonic rat dorsal root ganglia neurons and inhibits evoked, but not basal, release of calcitonin gene-related peptide (cGRP) from primary cultures of rat trigeminal ganglia.<sup>20-22</sup> In rat in vivo models of inflammation, pretreatment of the rat hind paw with BoNT/A (Botox), prior to carrageenan challenge significantly reduced the amount of edema formation.<sup>23</sup> A rat formalin in vivo model further demonstrated that pretreatment with BoNT/A led to inhibition of glutamate release at the periphery and centrally, and a decrease in wide dynamic range activity and c-fos expression.<sup>24</sup> These in vitro and in vivo data suggest that BoNT/A might affect neurogenic inflammation by directly affecting release of peripheral pain mediators involved in peripheral sensitization, leading to an indirect reduction in central sensitization at the spinal cord level.<sup>24</sup>

To our knowledge, this was the first study on the use of BoNT/A in patients with provoked vestibulodynia to suggest that the mechanisms for the relief of patients' pain are due to the combined effects of muscle relaxation (inhibition of acetylcholine release at alpha and gamma motor neurons) and the inhibition of release of neurotransmitters that cause pain and inflammation (substance P and cGRP). In this study, all patients had relief of their symptoms following BoNT/A injections. The duration of relief was dependent on the dose (higher dose, longer duration). None of the study participants experienced adverse effects as a result of the treatments. We are continuing to evaluate the optimal dose and injection technique and any additive effects of BoNT/A in our patients. Based on our current findings and the findings of others, a double-blind, placebo-controlled trial to evaluate the efficacy of BoNT/A in treating patients with vulvodynia is warranted and currently under way.

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