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**Does Botulinum Toxin A Injections Into The Pelvic Floor Muscles of Women with Chronic
Genitopelvic Pain and Vaginal Spasm Improve Pain and Sexual Functioning?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

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Abstract

OBJECTIVE: The objective of this evidenced based medicine review is to determine whether or not botulinum toxin A injections into the pelvic floor muscles of women with chronic genitopelvic pain and vaginal spasm improve pain and sexual functioning.

STUDY DESIGN: Review of two double blind randomized controlled trials and one case series from peer reviewed journals published between 2006-2011.

DATA SOURCES: Two randomized controlled trials and one case series were found using PubMed, Google Scholar, and Cochrane Library.

OUTCOMES MEASURED: All three studies measured pain and sexual functioning using self-reported surveys including the visual analog scale for pain, Female Sexual Functioning Index, and Sexual Activity Questionnaire.

RESULTS: Petersen et al. determined that botulinum toxin injections into the vulva did not improve pain or sexual functioning in vestibulodynia patients when compared to the control group. Similarly, Abbott et al. found that botulinum toxin injections into the pelvic muscles for chronic pelvic pain did not improve pain or sexual functioning when compared to the control group. In the case series conducted by Pelletier et al., botulinum toxin injections into the vulva reduced pain and improved sexual functioning for vestibulodynia patients.

CONCLUSION: Botulinum toxin type A injections into the pelvic floor muscles are not an effective form of treatment for chronic pelvic pain or vestibulodynia. Both randomized controlled trials contributed the improvement in the control group to the placebo effect, among other theories. In the future, randomized controlled trials should use a larger sample size and include a nocebo group to further elaborate on the above results.

KEY WORDS: Provoked Vestibulodynia, Botulinum Toxin, Chronic Pelvic Pain

INTRODUCTION

Chronic pelvic pain is defined as noncyclic pain localized to the genitopelvic area for greater than three months that causes the patient functional disability and is not related to pregnancy.¹ Common symptoms of chronic pelvic pain are muscular spasm and dyspareunia.¹ Chronic pelvic pain is a broad term and is commonly found to be a symptom of an underlying pathologic condition. The various causes of chronic pelvic pain including endometriosis, adenomyosis, pelvic inflammatory disease, irritable bowel syndrome, interstitial cystitis, and depression, are too numerous to discuss for the purposes of this paper.¹ For simplicity, provoked vestibulodynia, a condition that can cause chronic pelvic pain, will be discussed. Vestibulodynia, otherwise known as vulvodynia, is chronic vulvar pain in women for greater than three months.² Provoked vestibulodynia refers to pain and spasm in the vulva and vagina after physical aggravation of the tissue, such as through tampon insertion or sexual intercourse.²

The prevalence of chronic vulvar pain is between 3-15%.² That number rises to 39% when considering chronic genitopelvic pain in women.¹ The prevalence of dyspareunia, one of the most common presenting symptoms of provoked vestibulodynia, is between 8-22%.³ Having to care for patients with vestibulodynia, chronic pelvic pain, or dyspareunia in practice is therefore quite possible. Alarming, reports have indicated that half of women with self-reported vulvar pain and two thirds of females with chronic pelvic pain will not seek medical attention, indicating prevalence may be under-reported.^{1,2} It is vital that members of the medical community remember to ask patients questions concerning these conditions during routine primary care or gynecological visits. However, those patients who do seek medical attention are having a significant impact on health care expenses. One study estimated that chronic genitopelvic pain cost the United States health care system 881.5 million dollars per year in

terms of outpatient visits alone.⁴ In this instance, discussing financial burden on the patient is appropriate, as well. Botulinum toxin injections for genitopelvic pain syndromes, including provoked vestibulodynia, are considered off-label uses.² Typically, the injections will be a direct out-of-pocket expense to the patient.² No documented number of vestibulodynia or chronic pelvic pain health care visits could be found for the purposes of this research paper.

The exact cause of provoked vestibulodynia is not known. One proposed theory is that pain in the vulva is generated as a result of compression of blood vessels and nerve fibers from pelvic floor hypertonicity and spasm.⁴ An initial insult to the vulva causes an overactive inflammatory response leading to proliferation of nerve fibers and central sensitization of pain.² Overactive nerves release excessive amounts of acetylcholine, causing hypertonicity and spasm.⁴ Other proposed theories include infection with *C. albicans*, vaginal allergy, hormone imbalance, genetic predisposition, and psychological dysfunction.² Notably, there is an association between provoked vestibulodynia and other hypersensitive pain syndromes, like irritable bowel syndrome and fibromyalgia.²

Diagnosis of provoked vestibulodynia is based on four factors: pain localized to the vulva, without identifiable cause, that has been present for greater than three months, and is worsened by pressure point testing.² A detailed history and physical, including inspection, palpation, speculum exam, and pressure point testing using a cotton-tipped applicator, are required for proper diagnosis.² Laboratory testing and diagnostic imaging should be done as needed to rule out identifiable causes.

Several treatments exist for vestibulodynia. Behavior modification, including proper vulvar hygiene, and pelvic floor physical therapy are mainstays of treatment encouraged in all patients.⁵ Cognitive behavioral therapy, topical lidocaine, and topical estradiol are considered

first line management.⁵ Second tier therapy consists of anti-depressants and neuropathic pain agents.⁵ Third tier treatment includes botulinum toxin injections, steroid injections, and gabapentin cream.⁵ Surgical intervention is last line therapy for severe cases of vestibulodynia refractory to the above-mentioned treatment options.⁵

Botulinum toxin type A is a relatively new treatment for vestibulodynia. The toxin relaxes hyperactive muscles by inhibiting exocytosis of acetylcholine, leading to muscle paralysis.⁴ Blood flow to the tissue improves, lessening painful stimuli.⁴ Botulinum toxin is believed to have some initial analgesic effect, as well, until paralysis is reached in approximately 2-3 days.⁴ This paper will evaluate the efficacy of botulinum toxin type A injections into the pelvic floor muscles of women with provoked vestibulodynia, and chronic genitopelvic pain, as an alternative treatment modality.

OBJECTIVE

The objective of this evidenced based medicine review is to determine whether or not botulinum toxin A injections into the pelvic floor muscles of women with chronic genitopelvic pain and vaginal spasm improve pain and sexual functioning.

METHODS

Three studies on the use of botulinum toxin type A injections as a treatment for provoked vestibulodynia and chronic pelvic pain in women greater than the age of 18 were selected for analysis. Petersen et al. and Abbott et al. are both double-blind, randomized controlled trials, while Pelletier et al. is classified as a case series. All three articles were published in English in peer-reviewed journals between 2006-2011. To find the above articles, key words “botulinum toxin,” “provoked vestibulodynia,” and “chronic pelvic pain” were searched in PubMed, Google Scholar, and Cochrane Library databases. Only relevant double-blind randomized controlled

trials that answered the above stated clinical question were included in the initial search. After only two relevant randomized controlled trials were found, the search was broadened to include non-randomized, non-controlled studies. A subsequent case series was found that was relevant to the proposed clinical question. Inclusion criteria for this analysis consisted of relevance to the clinical question and whether or not patient oriented outcomes were measured. Studies were excluded if outcomes measured were not patient oriented. Statistics utilized in the above studies include: number needed to treat (NNT), p-values, and mean change from baseline.

Table 1: Demographics and characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Petersen, 2009 ⁶	Double Blind RCT	64	>18 years old	symptoms of provoked vestibulodynia for more than 6 months; diagnosis of provoked vestibulodynia according to Friedrisch criteria; ability to read and understand Danish language; use of safe contraception (oral contraceptives, intrauterine device, Nuvaring®) sterilization, or hysterectomy for the first 6 months after inclusion treatment (barrier methods were not acceptable forms of safe contraception)	previous treatment with Botox in the genitalia; ongoing infection in the vulva or pelvis; skin disease in the vulva; pregnancy; major medical or psychiatric illness (diagnosed with depression, and/or in medical treatment for depression of schizophrenia); peripheral motor neurological disease (myasthenia gravis, amyotrophic lateral sclerosis, or Lambert-Eaton syndrome); diabetes; use of calcium-antagonists, aminoglycosides, magnesium sulfate, or systemic or topical steroids; concurrent medical, physical, psychological, or sexual therapy within the first 6 months of their participation in this study; age less than 18	4	.5 mL of solution (20 units of botulinum toxin A diluted in saline) injected symmetrically into the bulbospongiosus muscles lateral to the meatus of the Bartholin's duct
Abbott, 2006 ⁷	Double Blind RCT	60	18-55 years old	female aged 18-55; 2 years of chronic pelvic pain that has disrupted daily activities; objective evidence of pelvic floor myalgia defined as the presence of contracted, painful muscles on palpation and elevated resting pressures (more than 40cm H2O) by vaginal manometry	inability to demonstrate pelvic floor spasm; breastfeeding, pregnant, or desire to become pregnant; unwilling to use contraception during the study; previous botulinum toxin A injections into the pelvic floor; palpable pelvic pathology; current use of aminoglycoside antibiotics; history of neurologic bleeding disorders; known sensitivity to botulinum toxin A	3	1mL solution (20 units botulinum toxin A diluted in saline) injected into two sites bilaterally within each puborectalis and pubococcygeus muscles under conscious sedation
Pelletier, 2011 ⁸	Case Series	20	18-60 years old	patients' refractory to other forms of treatment for vulvodynia (TCAs, biofeedback, counseling); pain triggered by nonallergic stimulus that is responsible for introital dyspareunia; post-menopausal or taking an effective form of contraception	positive serological evidence for HIV or <i>Chlamydia trachomatis</i>	0	1mL solution (50 units of botulinum toxin A diluted in saline) injected into the right and left bulbospongiosus muscles under EMG monitoring

OUTCOMES MEASURED

Pain and sexual functioning were the patient-oriented outcomes measured in each of the three articles. Pain was measured in all three studies using the visual analog scale (VAS). Participants choose a number between 1-10 that best reflects their pain level, '0' indicating no pain and '10' indicating intensely severe pain. Pelletier et al. assessed pain prior to the botulinum injections and then re-assessed at 3 and 6 months post-injection.⁸ Petersen et al. assessed similarly, but included re-assessment at 12 months, as well.⁶ Abbott et al. re-assessed at 2, 4, 8, 12, 16, 20, and 26 weeks post-injection.⁷

Two questionnaires were utilized to assess sexual functioning. Petersen et al. and Pelletier et al. used the Female Sexual Functioning Index (FSFI). This is a self-report survey where females answer 19 questions about their sexual functioning over the past 4 weeks. Questions cover six main categories: desire, arousal, lubrication, orgasm, satisfaction, and pain. Responses are rated from 0-5 or 1-5 and added together. The cut off is a score <26, which indicates a risk for sexual dysfunction. The higher the score, the less likely a female is experiencing sexual dysfunction. Again, Pelletier et al. and Petersen et al. assessed sexual functioning before the injections were given and used the same time frame listed above for re-assessment post-injection.^{6,8} Abbott et al. used a Sexual Activity Questionnaire (SAQ) to measure sexual functioning.⁷ Participants answer questions using the 4-point Likert scale⁹ on sexual function in relation to pleasure, discomfort, and habit.⁷ Responses allowed researchers to quantify how many women were experiencing or not experiencing certain sexual issues. Questionnaires were completed before the injections were given and then again at 4, 12, 16, 20, and 26 weeks post-injection.⁷

RESULTS

Two randomized controlled trials and one case series concerning the use of botulinum toxin type A as a novel treatment option for women greater than 18 years old with provoked vestibulodynia or chronic pelvic pain were analyzed for the purpose of this paper. All studies took place in outpatient gynecology settings.^{6,7,8}

Petersen et al. began their study by screening 164 women using the inclusion criteria listed in Table 1.⁶ Originally, 65 women were included in the study, but one participant was excluded on the day of the injections for an active vulvar infection.⁶ Women were randomly assigned to either the botulinum toxin group (B group) or the placebo group (P group).⁶

In terms of pain reduction, there was no significant difference reported between the two groups at 6 months follow up ($p > 0.05$).⁶ However, there was a significant difference in pain reduction at 6 months within each group.⁶ The mean change from baseline for the B group at 6 months follow up was -2.3 ($p < 0.001$), while the P group was -2.5 ($p < 0.001$).⁶ At baseline, 89% of patients in the B group and 100% of patients in the P group scored below at 26.55 on the FSFI, indicating sexual dysfunction.⁶ At 6 months, scores improved with researchers reporting a mean change from baseline of -10% in the B group and -14% in the P group.⁶ The improvement in sexual functioning was not significant between the two groups ($p = 0.635$).⁶ Sexual activity was used as a means to assess the efficacy of the botulinum toxin injections, as well.⁶ The researchers reported their findings as dichotomous data, and therefore NNT could be calculated using the information in Tables 2 and 3. The NNT to allow sexual activity in patients abstaining from sexual activity because of provoked vestibulodynia was -5.⁶ This means that for every 5 women treated with botulinum toxin for provoked vestibulodynia, 1 fewer woman would be sexually active than when compared to placebo.⁶ This data was found to be significant ($p = 0.022$), and to have a large treatment effect, as only 64 women were enrolled in the study.⁶

In total, four women were lost of follow up during the study: two were excluded at 3 months for topical lidocaine use, one withdrew at 4 months, and one was excluded at 5 months due to pregnancy.⁶ Adverse events reported by participants included tenderness at the injection site, flu-like symptoms lasting 12-24 hours post-injection, muscle weakness, and issues achieving orgasm.⁶

Table 2: Participants sexually active at 6 months, Petersen et al.⁶

	Botulinum toxin group	Placebo group	p-value
% sexually active at 6 months follow up	83%	100%	0.022

Table 3: Calculations for Petersen et al.⁶

Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
-0.17	-0.17	-5

Abbott et al. began their study by screening 401 potential participants over the phone.⁷ In total, 118 women were assessed, and 60 women met the criteria to participate in the study.⁷ They were subsequently randomized into two groups, the Botulinum toxin (BOTOX) group and the placebo group.⁷

Again, there was no significant difference in VAS scores when compared to the placebo group at the conclusion of the study.⁷ However, VAS scores did decrease for both groups throughout the follow up process.⁷ Results from the SAQ are listed in Tables 4 and 5. No significant mean change from baseline was reported between the BOTOX group when compared to control for each section of the SAQ.⁷ There was no significant mean change from baseline within each group either.⁷

In total, one woman was lost to follow up and two women withdrew from the study.⁷ Reported adverse events included: cold/flu-like symptoms, bleeding at the injection site, headache, pelvic/back pain, and gastrointestinal upset.⁷ Events occurred in both groups.⁷

Notably, two members of the BOTOX group experienced urinary and fecal incontinence after the injections, which slowly resolved over a few months.⁷

Table 4: Mean change in SAQ responses, BOTOX group, Abbott et al.⁷

SAQ sections	BOTOX group at baseline	BOTOX group at 26 weeks	Mean change from baseline	p-value
Pleasure	9	11.5	+1.5	Not significant
Habit	1	1	0	Not significant
Discomfort	3	2	-1	Not significant

Table 5: Mean change in SAQ responses, Placebo group, Abbott et al.⁷

SAQ sections	Placebo group at baseline	Placebo group at 26 weeks	Mean change from baseline	p-value
Pleasure	8	10	+2	Not significant
Habit	1	1	0	Not significant
Discomfort	5	2	-3	Not significant

Pelletier et al. enrolled 20 women with provoked vestibulodynia.⁸ As reported in Table 6, a significant number of women were able to have sexual intercourse at 3 months when compared to baseline.⁸ Mean change from baseline in both VAS and FSFI scores, as reported in Table 7, were also found to be significant when compared to baseline.⁸ Authors reported no adverse effects from the botulinum toxin treatment except pain at the injection site and flu-like symptoms post-injection.⁸

Table 6: Participants able to have sexual intercourse, Pelletier et al.⁸

Sexual intercourse possible at baseline (N, %)	Sexual intercourse possible at 3 months (N, %)	p-value
2, 10%	13, 65%	<0.001

Table 7: Mean change in VAS and FSFI scores, Pelletier et al.⁸

	Baseline	3 months	Mean change from baseline	p-value
Average VAS score	8.37	2.57	-4.47	<0.001
Average FSFI score	3.74	18.44	+16.42	<0.001

DISCUSSION

Both randomized controlled trials concluded that botulinum toxin injections produced no significant changes in pain or sexual functioning when compared to the control group.^{6,7} However, the experimental and control groups in both studies documented improvement in pain and sexual functioning scores throughout the follow up process.^{6,7} Petersen et al. attributed the improvement of the control group to placebo effect and postulated that the success of various case series might be due to this, as well.⁶ Alternatively, the natural progression of the disease may lead to improvement overtime, which is potentially why both groups improved in a similar fashion.⁶ Abbott et al. agreed that the placebo effect could be why no significant changes are noted between groups, but also hypothesized that improvement in the control group could be due to the effects of muscle needling.⁷ Injections into the muscle with saline could have desensitized trigger points, leading to decreased muscle spasm and pain, similar to the effects of acupuncture.⁷ The case series by Pelletier et al., however, reported significant improvement in pain and sexual functioning among participants.⁸

Still, limitations exist in the above three studies, including the relatively small sample size used by all.^{6,7,8} Petersen et al. admit that the low dosage of botulinum toxin used in their trial and the lack of evaluation of pelvic floor tonus were issues present in the study design.⁶ Also, 56% of participants were taking OCPs throughout the study and the affect the additional hormones could have had on the outcomes is uncertain.⁶ Abbott et al. was unclear about how questionnaires were scored and was limited in their discussion of the results leaving much of the analysis to the reader.⁷ Pelletier et al. only had fifteen women fill out the FSFI and never commented on why five women were excluded from analysis.⁸

Botulinum toxin injections, as reported above, are not typically covered by insurance companies.² Not only are injections typically paid for by the patient but locating a practitioner

who will perform the injections is also difficult.² Adverse effects of botulinum toxin injections into the pelvis are not well documented, either. Flu-like illness, weakness, bruising or bleeding at the injection site, transient numbness, headache, and malaise are some potential side effects.¹⁰

Considering this and the data from the above randomized controlled trials that indicate botulinum toxin injections into the pelvis do not improve pain or sexual functioning, practitioners should not recommend this line of treatment for patients with provoked vestibulodynia.

CONCLUSION

As evidenced above, botulinum toxin type A injections into the pelvic floor muscles are not an effective form of treatment for chronic pelvic pain or vestibulodynia. However, very few randomized controlled trials exist concerning the use of botulinum toxin injections for genitopelvic pain syndromes. Continuing to study the use of botulinum toxin as a treatment option is therefore vital. Using larger sample sizes, higher concentrations of botulinum toxin, and studying objective evidence of pelvic floor pain and spasm will improve the quality of data produced by future studies. Using a standardized technique to deliver the injections will allow easier comparison between research studies, as well. Lastly, further research into acupuncture and trigger point release as treatment options for chronic pelvic pain and provoked vestibulodynia could prove beneficial to patients in the future.

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