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Review Article

The Use of Botulinum Toxin in the Pelvic Floor for Women with Chronic Pelvic Pain–A New Answer to Old Problems?

Jason Abbott, B. Med (Hons), MRCOG, FRANZCOG, PhD*

From The School of Women's and Children's Health, University of New South Wales, Sydney, Australia.

ABSTRACT Chronic pelvic pain occurs in about 15% of women and has a variety of causes requiring accurate diagnosis and appropriate treatment if pain reduction is to be effected. Superficial conditions such as provoked vestibulodynia and deeper pelvic issues such as pelvic floor myalgia were traditionally difficult to diagnose and adequately treat. For provoked vestibulodynia, there are limited data, in the form of case reports and small series, to indicate that botulinum toxin (BoNT) injections may provide short-term (3–6 months) benefit. Retreatment is reported to be successful and side effects are few. Class-I studies are essential to adequately assess this form of treatment. For pelvic floor myalgia, 1 class-I study and 3 class-II to -III studies indicate efficacy of BoNT. In the only double-blind, randomized, controlled study, significant reduction in pelvic floor pressures with significant pain reduction for some types of pelvic pain are reported compared with baseline. No differences in pain occurred compared with the control group who had physical therapy as an intervention. Physical therapy should be used as a noninvasive first-line treatment, with BoNT injections reserved for those who are refractory to treatment. Pelvic floor disorders should be considered as a cause for chronic pelvic pain in women and an attempt made to diagnose and treat such problems as a routine practice. The use of BoNT as a therapeutic option for pelvic floor muscle spasm and pain is still in its infancy. Initial reports suggest that there may be a significant role for women with chronic pain that is refractory to currently available medical and surgical treatments, however, there are very few high-quality studies and research is essential before this novel treatment can be accepted into widespread use for pelvic pain attributable to the pelvic floor. Journal of Minimally Invasive Gynecology (2009) 16, 130–135
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Chronic pelvic pain is estimated to affect 15% of women aged 18 to 50 years [1]. Women with pelvic pain symptoms may have 1 or more of a diverse group of problems that require correct diagnosis and appropriate treatment for the symptoms to be controlled. A female preponderance exists for pelvic pain, with 3 times as many women as men with these symptoms [2].

For women with pelvic pain, considerable emphasis is placed on diagnosis by visualization at laparoscopy, where problems such as endometriosis, endosalpingiosis, pelvic adhesions, and postinflammatory changes may be identified and treated. If visible disease is not present, or if it is present but its removal is only partially effective or ineffective, then the patient may be considered to have psychogenic pain [3] or dismissed without consideration of further investigation. The complex muscular system in the pelvis that contributes to functions such as defecation, micturition, sexual intercourse, and obstetric delivery is often overlooked as a possible cause for pain, although it is recognized that relief of muscle spasm is associated with relief of pain symptoms [4].

Once a diagnosis of possible pelvic floor spasm as a contribution to chronic pain is made, objective measurements and physical therapy as a method of low-risk treatment is a logical, inexpensive, and nonsurgical approach to treatment [5]. The contract/relax treatment model reduces the resting tone of the pelvic floor muscles and disrupts the spasm cycle, alleviating pain. The addition of biofeedback provides the patient with objective information regarding the adequacy of pelvic floor training, and objective assessment of the changes in baseline tone and strength for the physician [5]. For patients in whom these treatments are not successful and who

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Corresponding author: Jason Abbott, B Med (Hons), MRCOG, FRANZCOG, PhD, School of Women's and Children's Health, University of New South Wales, Barker Street, Randwick, New South Wales 2031, Australia.
E-mail: j.abbott@unsw.edu.au

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continue to have pain symptoms, treatment with botulinum toxin (BoNT) may be considered if there are appropriate indications.

Botulinum toxin is a potent neurotoxin produced by the bacterium *Clostridium botulinum*, a gram-positive, spore-forming organism. The toxin is the most poisonous naturally occurring substance known. When injected for therapeutic purposes it binds to peripheral nerve terminals and prevents release of acetyl choline into the synaptic cleft, leading to muscle paralysis [6]. There are 5 known subtypes of exotoxin categorized A to E, depending on the toxin's immunologic specificity. Types A and B are currently the only commercially available subtypes. The clinical effect of the toxin is dose related and these effects decline as presynaptic molecules turn over and neural sprouts develop from the toxin-affected axonal terminal to create a new functional synapse [7]. Such changes allow target muscle cells to recover and return to normal contractility.

Botulinum toxin has been used clinically for cosmetic applications [8], focal dystonias [9], vocal cord dysfunction [10], and muscle spasticity associated with stroke [11]. In the last 2 decades, increased use of BoNT for muscular and inflammatory conditions occurred [12,13]. In the pelvis, BoNT is used in conditions such as pelvic pain caused by muscle spasm [5,14], provoked vestibulodynia [15], detrusor overactivity [16], detrusor sphincter dyssynergia [17], chronic anal fissure [18], and chronic constipation [19].

The first report using BoNT as a treatment for chronic pelvic pain occurred more than 10 years ago for the difficult problem of vaginismus [20]. Since this initial report, surprisingly few data were reported to support this treatment, with only a handful of methodologically sound, randomized controlled trials (RCTs) performed and published.

In writing this review, the following electronic databases were used from inception through July 2008: CINAHL, EMBASE, and MEDLINE. We used the following Medical Subject Heading terms and keywords: ''chronic pelvic pain,'' ''pelvic floor myalgia,'' ''provoked vestibulodynia,'' ''vaginismus,'' ''botulinum toxin,'' and ''gynecological pain.'' Only published data were reported, with abstracts and incomplete studies not included in this review.

The Pelvic Floor Muscles as a Source of Chronic Pelvic Pain in Women

History and physical examination underpins diagnosis and treatment of chronic pelvic pain. The use of noninvasive imaging such as ultrasound may not help to diagnose the specific problem but is useful in excluding structural pathology. Given that a dynamic relationship exists between different systems that all converge in the pelvis, such as the gastrointestinal, urologic, and genital tracts, pathology in this area may have a variety of symptoms, and often considerable overlap occurs between symptoms arising from these body systems.

Gynecologists are familiar with the assessment and treatment of pelvic floor laxity, but have very limited knowledge in the assessment and treatment of pelvic floor spasm for gynecologic symptoms. The levator ani are skeletal muscle and are subject to spasm that cause pain and is reported in other areas of the body [21–23]. The use of BoNT into muscles in spasm is reported to relieve the spasm and reduce pain in other skeletal muscles, although there are limited data in the pelvic floor [5,14,24].

The first reported use of BoNT in the pelvic floor was a pilot study involving 12 women with chronic pelvic pain for more than 2 years, previous failed physical therapy, and medical treatments with objective evidence of pelvic muscle spasm by vaginal manometry. These women were treated with 40 U of BoNT/A (Botox, Allergan, Gordon, Australia) injected into the puborectalis and pubococcygeus under conscious sedation [5]. The women were reassessed by visual analog scale (VAS) scores for dysmenorrhea, nonmenstrual pelvic pain, dyspareunia, and dyschesia at 2, 4, 8, and 12 weeks postinjection. The study reports significant reduction in dyspareunia (VAS 80 vs 28, $p = .01$) and dysmenorrhea (VAS 67 vs 28, $p = .03$) scores, with nonsignificant improvements in dyschesia and nonmenstrual pelvic pain.

This short-term, uncontrolled study was methodologically sound, however, the small number of patients and possible placebo effect limit its generalizability. Patients refractory to most other standard treatments were recruited in the study and this limits the external validity of this study. However, the results of this study provide the first class-II evidence for improvement in chronic pelvic pain after injection of BoNT into the pelvic floor muscles.

A larger class-III study was reported, in which 67 women with a combination of experiences, all having sexual dysfunction classified as either lifelong vaginismus or lifelong or secondary dyspareunia complicated by vulvar vestibulitis, were treated with BoNT/A. Injections of 20 U every 2 to 3 months into the levator ani [24] were given and symptom reduction was reported to be 46% to 76%, depending on the subgroup, with a cure rate of 20% to 46% and a mean number of 2.4 injections. This is a larger group of women with good reported outcomes; however, the uncontrolled nature and patient heterogeneity in the study are again limiting factors.

A retrospective study of 24 women (mean age 24 years) specifically investigated the treatment of moderate and severe vaginismus [25]. Botulinum toxin A (150–400U) was injected into the puborectalis muscles in 3 sites bilaterally. At 1 week postprocedure 23 (95.8%) patients were reported to have little or no vaginismus, 18 (75%) were able to have intercourse after 1 injection, and 4 (16.7%) had mild pain. One woman reported no change after injection. Patients were followed for a mean of 12.3 months (range 2–24 months) with no reported recurrence. The retrospective nature of this study limits its conclusion, although it does infer some benefit for this patient population.

One double-blind, randomized, placebo-controlled study reported women having injections of BoNT to the pelvic

floor for chronic pain [14]. A total of 400 women were screened, 68 met the entry criteria, 8 declined participation, and 60 were randomized into the study. The 2 study groups were 30 women receiving 80 U of BoNT/A and 30 receiving placebo injections of saline. Entry criteria included women aged 18 to 55 years with chronic pelvic pain of greater than 2 years and physical examination and perineometry using a vaginal manometer identifying them as having objective evidence of pelvic floor muscle spasm. The vaginal manometer is reported to be both a valid and reliable indicator of pelvic floor pressure [26].

In this study, women were not required to undergo a physical therapy program for treatment of their pelvic pain. The duration of follow-up was 6 months with 8 visits during that time for pain assessments, completion of validated quality-of-life instruments, and assessment of pelvic floor pain and pressure by both digital examination and perineometry. The interventions were 80 U of BoNT/A at a concentration of 20 U/mL equally divided into 8 injection sites in the puborectalis and pubococcygeus bilaterally for women in the BoNT/A group or saline injections into each of the sites for women in the placebo group. Injections were done using a palpation technique [5] without electromyography (EMG) and under conscious sedation. The study was methodologically rigorous with excellent follow-up.

The primary outcome of the study was a decrease in pain symptoms and the results at 6 months indicated that pain scores were reduced for both groups in all parameters, consistent with expected reductions in placebo groups as evidenced in other placebo-controlled studies. Although pain scores in the BoNT/A group were generally lower, no statistically significant intergroup differences occurred. When compared with baseline, significant intragroup differences occurred in the BoNT/A group for nonmenstrual pelvic pain and dyspareunia (VAS 51 vs 22, $p = .009$, and VAS 66 vs 12, $p = .001$, respectively). In the placebo group, only dyspareunia was significantly reduced (VAS 64 vs 27, $p = .043$).

Pelvic floor pressures were significantly different between the 2 groups after injection and up to 16 weeks of follow-up when the BoNT-treated group had a slow increase in pressure to 6 months, although values did not return to baseline. Significant decrease occurred in pelvic floor pressures in the BoNT group from baseline (49 vs 32 cm H_2O, $p = .001$) and a smaller, but still significant reduction in pelvic floor pressures in the placebo group (44 vs 39 cm H_2O, $p = .003$).

Despite a rigorous methodology and pain reduction similar to that shown in the pilot study by the same group of authors, no significant difference occurred in pain scores between the BoNT group and the placebo group. Such findings may be a result of the placebo group receiving an important intervention in the form of physical therapy. In the pilot study, women were required to have failed physical therapy, but this was not required in the RCT, a decision made to broaden the entry criteria to the study with the view to improving external validity. The reduction in pelvic pressures and greater control of the pelvic muscles in women in the placebo group was evident with reduced resting tone and improved maximum contraction pressures. The conclusion is that physical therapy should be first-line management for this indication, with BoNT reserved for refractory cases.

For women with pelvic floor muscle spasm, there is sound, but not irrefutable, evidence that BoNT injections are helpful for those who have selected symptoms, with daily pelvic pain and dyspareunia being the symptoms likely to be improved by treatment. Reported side effects are minimal, but further research is required before treatment can be recommended on a wider scale. Botulinum toxin significantly reduces pelvic floor muscle pressures, which can be associated with pain for some women. Because of the intensive nature of physical therapy, repeated visits, and the need for cooperation and compliance of patients, it is unclear at this time whether physical therapy is a more cost-effective treatment than BoNT for women with pelvic floor muscle spasm and pelvic pain.

Provoked Vestibulodynia and Other Causes of Chronic Pelvic Pain with Possible Involvement of the Pelvic Floor

Vulvodynia is the symptom of pain in the vulval area. It may occur as generalized or localized, spontaneous or provoked pain [27]. Vulvodynia is not a diagnosis in itself and represents pain of unknown origin, although vulval dermatoses, inflammatory conditions, or muscular conditions may be present, whether they can be proved or not. Provoked vestibulodynia is pain in the vaginal vestibule that occurs after any kind of stimulation, from the touch of clothing to examinations and intercourse. It is hypothesized that vestibulodynia may result from intraepithelial neural hyperplasia with subsequent activation of the nociceptors in this area [28,29]. Usual treatments for these superficial painful symptoms include physical therapy and biofeedback, local application of cold, medical treatment with tricyclic antidepressants, topical anesthetics, local steroidal injections, and excision surgery of the vulva [30,31].

There are few data that report the use of BoNT in the treatment of vulvodynia or provoked vestibulodynia. Some of these studies indicate a possible contribution of pelvic floor muscle involvement with pelvic pain. A pilot study of 12 women with provoked vestibulodynia was reported where the first 7 women recruited received 35 U of BoNT/A injected in 3 to 4 painful sites under the vulvar epithelium [15]. Follow-up was at 1 and 3 months, and/or when the pain returned to baseline. All of these women and a further 5 women were injected with 50 U of BoNT/A when pain returned to baseline in the first group. The VAS pain scores were significantly decreased in the 35U and 50U groups at 30 days (VAS reduced 8.1–2.9 and 7.4–1.8, respectively, $p < .0001$). The duration of effect was 8 weeks and 14 weeks in the 2 cohorts and no side effects were reported.

Women in this study were homogenous with defined entry criteria regarding pain symptoms and a robust methodology and outcome measures. However, it remains a small,

uncontrolled study that limits conclusions. The study does provide reasonable evidence that pain of a vulvar origin may be effectively treated by BoNT injections. The authors of the pilot study indicate that they are conducting a RCT that should provide valuable information in this important area of pelvic pain.

A smaller study reports outcomes for 7 women with intractable genital pain treated with BoNT/A in 20U aliquots injected at each pain site [32]. The authors report an improvement in VAS pain score after treatment from 8.3 to 1.4. Patients were assessed at 2 weeks and a repeated injection of 40 U was administered if the first treatment was not successful. Of the 7 women, 5 required a second injection and were followed up for a mean of 11 months without recurrent symptoms.

This is a heterogeneous group of women, with BoNT/A injected into different anatomic areas including the vaginal vestibule, the perineal body, and the levator ani. This variety of treatment sites indicates multiple diagnoses and comparison with any 1 group is difficult, if not impossible from this study. Although this study suggests that a variety of gynecologic conditions may be successfully treated by injections of BoNT, numbers for any 1 condition are very small and the limiting methodology provides little generalizable information [32].

There remain a small number of case reports on women diagnosed with vulvodynia/provoked vestibulodynia treated with BoNT/A dosages between 10 and 100 U with improved symptoms after injection [20,33–36]. Because of the varied methodologies and BoNT dosages used in these case reports, they contribute little further information on their own. The addition of all of this information does indicate that further evaluation may offer a new modality of treatment for women with pain in this area and it is essential that studies are undertaken to validate success or failure, side effects, and expected outcomes for patients before it should be offered as a therapeutic choice. Table 1 summarizes the evidence for BONT use in the pelvic floor.

Methods to Aid Placement of BoNT in the Pelvic Floor

Accurate placement of BoNT into the target tissue is essential for the clinical effects of the toxin to be apparent. For gynecologic indications, the more superficial problem of provoked vestibulodynia is best diagnosed in a patient who is awake with guidance from them. Evidence produced to date indicates that injection into the most painful areas on clinical examination produces appropriate clinical outcomes, although data are limited and further evidence is required. For deeper structures such as the pelvic floor muscles, EMG was used by some authors [24,33], although other experience indicates that no benefit exists from this technique, with significant pain for the patient during the procedure [5,14]. The palpation technique reported by these authors has revealed accurate placement with the appropriate and desired effect in muscles, with minimal side effects or complications. Muscle relaxation was almost universally noted and sustained, with temporary paralysis of the pelvic floor muscles achieved. Pelvic floor muscles that are in spasm are easy to palpate compared with a normal pelvic floor and injection into the muscles often produces a provoked muscular contraction that confirms correct needle placement. Results from the RCT [14] report significant differences in muscle tone and contractile power compared with placebo injections, confirming that this technique allows for appropriate and correct placement.

Ultrasound is an imaging technique very familiar to the gynecologist and was reported to be of benefit to correct needle placement in deep structures of the pelvis for needling purposes, including BoNT injection [37]. Although it is possible that this imaging modality may be helpful in localization of muscles and needle placement, there are limited data to support its use [19]. When BoNT is injected for puborectalis syndrome causing pain or outlet type constipation [19,38], transrectal ultrasound is reported to achieve a high rate of success as a result of muscle localization. Because men and women are treated and men do not have the advantage of a natural orifice for muscle localization and entry site for needling, this is likely to be necessary. In addition, puborectalis syndrome in its pure form is often managed by gastroenterologists rather than gynecologists, with the former specialist unlikely to be as familiar with digital pelvic examination even in female patients.

For more superficial pelvic pain issues such as provoked vestibulodynia, it seems unlikely that either ultrasound or EMG would have a significant impact on improving outcomes. Investigation of ultrasound localization of the pelvic floor muscles, perhaps both for diagnostic purposes and then as a therapeutic guide for needle placement, is warranted. For women, class-I evidence exists that pelvic floor muscle injection is adequate with a simple palpation technique. It is important to recognize that any additional imaging technique will require greater skill and incur increased cost. As such, it must offer a significant advantage over clinical examination and digitally guided placement to be considered routine practice.

Side Effects and Complications of BoNT Injections to the Pelvic Floor Muscles

There are few reported complications of the injection technique itself, although local bleeding and hematoma were reported [5,14]. Toxin reactions may also occur, however, class-I evidence exists using 80 U of BoNT/A for chronic pelvic pain in women reporting no difference in reported flu-like illness, gastrointestinal, neurologic, or musculoskeletal side effects compared with placebo [14]. There appears to be a dose-related effect, however, and treatment with high doses of BoNT ($\geq$200 U) is thought to increase the risk of toxin reaction [39].

Loss of pelvic sphincter control is reported [14], with women who have had previous issues with stress urinary

Table 1
Summary of evidence using botulinum toxin in the pelvic floor

Authors	Class(I–IV)	Size(n =)	BoNT/A dose (U)	Outcome measuresand significance	Comments
Pelvic floor muscle spasm					
Abbott et al [14]	I	60	80	Dyspareunia reduced VAS 66 vs 12 (p <.001); nonmenstrual pelvic pain reduced 51 vs 22 (p =.009); no significant difference between groups for pain, significant reduction in pelvic floor pressure	Physical therapy as first-line treatment; BoNT second-line treatment
Jarvis et al [5]	II	12	40	Dyspareunia reduced VAS 80 vs 28 (p =.01); dysmenorrhea reduced 67 vs 28 (p =.03); 25% reduction in pelvic floor pressures at 3 mo (p <.0001)	Good treatment for refractory pelvic pain
Bertolasi et al [24]	III	67	20	46%–76% Symptom improvement; 20%–46% cure rate	1–5 BoNT treatments every 3–4 mo; variable experiences
Ghazizadeh and Nikzad [25]	III	24	150–400	95% Tolerated vaginal examination; 75% tolerated intercourse	No recurrence at 12 mo, 2 women remained apareunic
Provoked vestibulodynia					
Dykstra and Presthus [15]	II	12	35	Pain scores reduced from 7.4 to 1.8; significant improvement in quality of life	Best evidence to date for possible treatment in provoked vestibulodynia
Yoon et al [32]	II	7	20–40	Pain scores reduced from 8.3 to 1.4; 5 women required second BoNT injection	Heterogenous group, possibly not all provoked vestibulodynia

BoNT = Botulinum toxin; VAS = visual analog scale.

incontinence likely to be more affected, but the possibility of fecal incontinence and inability to control flatus will usually be of more concern to women, and are likely to be temporary [14,40]. However, long-term fecal incontinence is reported with injection of BoNT directly into the external anal sphincter [41].

Repeated injections may lead to the development of secondary treatment failure as a result of antibody production that is reported in other clinical indications for BoNT [42]. Finally, the indications for BoNT discussed in this review represent off-label use of BoNT and informed consent including the potential risk of complications, both known and possible, needs to be obtained before therapeutic injection of BoNT into the pelvis can be undertaken.

Conclusion

Chronic pelvic pain in women is a common problem. Pelvic floor muscles spasm as a cause of chronic pain is recognized and its presence should always be included in the assessment of patients with chronic pelvic pain. Simple treatments such as physical therapy should be undertaken as an inexpensive and effective noninvasive intervention. Botulinum toxin may be used as a second-line treatment where physical therapy for pelvic floor involvement was not successful. Surgical intervention by laparoscopy should be used judiciously and the role of surgery considered in light of its expense and invasiveness compared with alternate treatments.

It is essential that high-quality, adequately powered studies are performed for new indications of BoNT in the pelvis and for additional studies to be performed for the treatment of pelvic floor muscle spasm because evidence for any type of chronic pelvic pain is limited to 1 class-I study. The role of surgery, expense, and patient satisfaction must be considered in all such future studies.

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