Botulinum toxin for chronic pelvic pain in women with endometriosis: a cohort study of a pain-focused treatment

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ABSTRACT

Background and objectives Many women with endometriosis continue to have pelvic pain despite optimal surgical and hormonal treatment; some also have palpable pelvic floor muscle spasm. We describe changes in pain, spasm, and disability after pelvic muscle onabotulinumtoxinA injection in women with endometriosis-associated pelvic pain, a specific population not addressed in prior pelvic pain studies on botulinum toxin.

Methods We present an open-label proof-of-concept case series of women with surgically diagnosed endometriosis. Under conscious sedation and with topical anesthetic, 100 units of onabotulinumtoxinA was injected transvaginally into pelvic floor muscle spasm areas under electromyography guidance. Changes in pain intensity, muscle spasm, disability, and pain medication use were assessed at periodic visits for up to 1 year after injection.

Results Thirteen women underwent botulinum toxin injection and were followed for at least 4 months. Before injection, 11 of the 13 women had spasm in >4/6 assessed pelvic muscles and reported moderate pain (median visual analog scale (VAS): 5/10; range: 2–7). By 4–8 weeks after injection, spasm was absent/less widespread (≤3 muscles) in all (p=0.0005). Eleven rated their postinjection pain as absent/mild (median VAS: 2; range: 0–5; p<0.0001); 7/13 reduced pain medication. Disability decreased in 6/8 women with at least moderate preinjection disability (p=0.0033). Relief lasted 5–11 months in 7 of the 11 patients followed for up to 1 year. Adverse events were mild and transient.

Conclusions These findings suggest pelvic floor spasm may be a major contributor to endometriosis-associated pelvic pain. Botulinum toxin injection may provide meaningful relief of pain and associated disability.

Trial registration number NCT01553201

INTRODUCTION

Chronic pelvic pain, defined as non-menstrual pelvic pain lasting for at least 6 months, affects 15%–25% of reproductive-age women.[1] Of women undergoing surgery for chronic pelvic pain, endometriosis is found in one-third.[2–4] Endometriosis, a chronic inflammatory condition, is commonly associated with pain and infertility.[5–7] In endometriosis, endometrial tissue from retrograde menstruation does not undergo apoptosis, but forms its own blood supply and innervation and grows outside the uterus on pelvic organs as estrogen-dependent, progesterone-resistant lesions.[8–11] Conventional treatment for endometriosis and its symptoms involves surgery to remove lesions and hormonal therapy to suppress lesion growth and often menstruation. However, for some women, even optimal treatment does not provide long-term relief of endometriosis-associated pain.[12–14]

Persistence of endometriosis-associated pelvic pain despite standard treatment cannot be explained by the physical lesions and surrounding hormone-sensitive inflammatory environment. It is more likely that, as in other chronic pain syndromes, peripheral and central nervous system sensitization perpetuates and may amplify pain after acute pain has resolved. Chronic myofascial dysfunction, which can manifest as taut bands of skeletal muscle that often contain myofascial trigger points (discrete, palpable, hyperirritable nodules), is associated with such sensitization. Active trigger points are spontaneously painful, and, when palpated, reproduce the patient's pain, possibly through visceral-somatic reflexes and convergence of innervation afferents on wide dynamic range neurons in the dorsal horn of the spinal cord. For example, relative to normal muscle tissue and non-spontaneously painful trigger points, active trigger point microenvironments have increased levels of sensitizing biochemicals, including calcitonin gene-related protein (CGRP) and substance P.[15] Thus, similar to other pain conditions, endometriosis-associated pain persisting after treatment likely involves peripheral and central sensitization as well as myofascial dysfunction.[16] Additionally, other factors such as depression, anxiety, and pain catastrophization (a trait associated with depression and anxiety) may contribute to the amplification and persistence of pain symptoms. In particular, pain catastrophization is associated with a lower likelihood of improvement from an intervention.[17]

Botulinum toxin is commonly used to manage hyperkinetic movement disorders and spasticity. Its efficacy in relieving pain associated with excessive muscle contraction led to its use in painful, non-movement disorder conditions such as migraine and postherpetic neuralgia, and in chronic pain management.[18] Botulinum toxin prevents acetylcholine release at nicotinic neuromuscular junctions, blocking synaptic neuromuscular transmission. Botulinum toxin also reduces release of pain mediators, including substance P and CGRP, which likely contributes to its ability to modulate pain.[19] Thus, botulinum toxin represents a promising treatment for active pelvic floor trigger points

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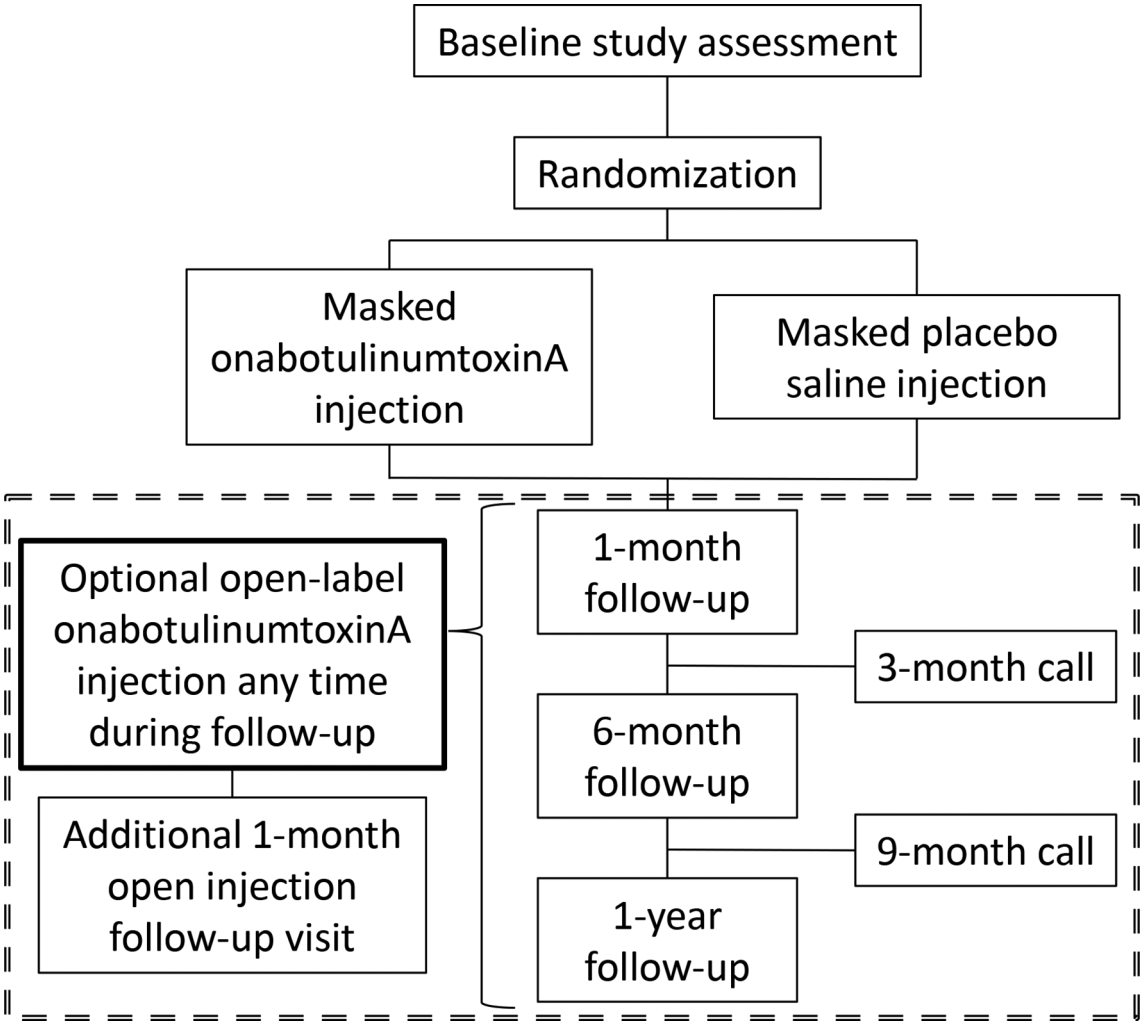

Figure 1 Study schema showing the sequence of randomized and open injections and follow-up assessments. Study schema for this case series was indicated within dotted line box.

contributing to endometriosis-associated pain refractory to surgical and hormonal treatment.[20]

Previous studies of botulinum toxin for treating chronic non-bladder pelvic pain, consisting largely of case series and case reports, suggest efficacy but have not specifically addressed women with endometriosis.[21–23] In this proof-of-concept case series, women with surgically diagnosed endometriosis and chronic pelvic pain persisting despite optimal surgical and hormonal treatments received an open-label onabotulinumtoxinA injection. Each of these women had pelvic floor muscle spasm that might be serving as a significant pain generator, perpetuating pain symptoms. We hypothesized that treating this pelvic floor spasm and pain with botulinum toxin might both ease spasm and lessen pain. The efficacy of botulinum toxin in these patients was assessed by measuring changes in pain intensity, muscle spasm, disability, and pain medication use over up to 1 year following injection.

METHODS

Participants

Women with endometriosis participating in a placebo-controlled study of botulinum toxin for chronic pelvic pain (figure 1) were offered an open onabotulinumtoxinA injection any time from 1 month to 1 year following the randomized, masked study injection. This case series reports on the outcome of these elective open injections. Patients were recruited nationally within the USA between July 2014 and June 2018; all study procedures were performed at the Clinical Center of the National Institutes of Health (NIH) in Bethesda, Maryland. Participants were recruited through the NIH patient recruitment office, online clinical trial posts, word of mouth, social media, and articles in the lay press.

Eligible women were aged 18–50 years with surgically diagnosed endometriosis and pelvic pain persisting for at least 3 months. All women had previously undergone conventional surgical treatment, had no current indication for endometriosis surgical treatment and had optimized hormonal management with their gynecologist. All were instructed to avoid initiating new pain management strategies and changes to hormone medications from at least 1 month prior to study enrollment until 1 month after the randomized study injection. Women were excluded if (1) their chronic pelvic pain could be primarily attributed to another cause, such as infection, gastrointestinal or psychological disorders, fibromyalgia, or chronic fatigue syndrome; (2) they had untreated severe cervical dysplasia or other gynecologic conditions, a history of urinary or fecal incontinence or known pelvic prolapse; or (3) they had undergone hysterectomy and bilateral salpingo-oophorectomy. Women were also excluded if they had an allergy to albumen or botulinum toxin or a known neuromuscular junction disorder such

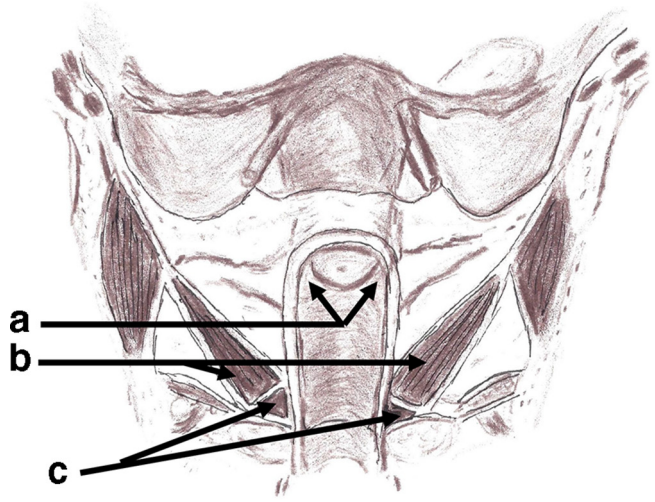

Figure 2 Coronal cross section of the female pelvis. Anatomic drawing of the female pelvis showing pelvic floor muscles targeted for transvaginal injection which include obturator internus, lateral to the uterine cervix (a), iliococcygeus, the lateral vaginal walls (b), and pubococcygeus, around the vaginal opening (c).

as myasthenia gravis or Lambert-Eaton syndrome. Women were not eligible if pregnant or lactating. Pelvic floor muscle spasm was required for inclusion. Women underwent an abdominopelvic pain-focused examination to determine the pattern and location of pelvic pain, to confirm the presence of pelvic floor muscle spasm and to assess whether palpation of the areas of spasm specifically recreated the spontaneous pain. Laboratory testing was performed to rule out pregnancy, sexually transmitted infections, severe cervical precancer and insufficiently treated hypothyroidism.

Written informed consent was obtained from all participants. All participants received the medication information guide for onabotulinumtoxinA (Allergan) and the study neurologist and gynecologist answered all participant questions prior to injection.

Design

On study enrollment, muscle spasm and pain was assessed with single digit intravaginal palpation of pubococcygeus, iliococcygeus, and obturator internus muscles bilaterally (figure 2). The presence and location of spasm was recorded. For the study's masked injection, eligible participants were randomized to receive either onabotulinumtoxinA or placebo saline injection into areas of pelvic floor spasm, as shown in study flow diagram (figure 1). Participants completed outcome assessments at 1 month after the masked injection with further follow-up evaluations every 3 months for 1 year following enrollment. After completion of the 1 month assessment for the masked injection, participants could opt to receive an open-label onabotulinumtoxinA injection at any time during the next year. All pelvic examinations and injections were performed by a gynecologist with 30 years of experience treating women with endometriosis and chronic pelvic pain. Response to the open injection was assessed 1 month later and at additional intervals timed to the masked injection, as described above.

When used for neurological indications, the effects of botulinum toxin are generally first noticed 1–2 weeks after injection, reaching a maximum about 4 weeks after injection. Benefit then gradually wanes, typically lasting about 3 months. In this study, we asked participants to maintain their usual medical management for pelvic pain from study enrollment until the 1 month assessment for the randomized injection. However, changes to pain management and hormone medications were permitted following the open injection to better reflect standard care of patients with endometriosis in the community. We prospectively recorded any changes in pain management or hormonal regimens.

Administration of onabotulinumtoxinA

Injections were targeted to the previously identified areas of muscle spasm that, when palpated, recreated the spontaneous pain (figure 2). Following the examination and 20 to 30 min before injection, participants were administered up to 10 mg oral diazepam and 4% lidocaine cream was applied to the vaginal mucosa over areas of spasm. Immediately prior to injection, the vaginal mucosa was cleansed with antiseptic to reduce risk of infection.

A 100-unit vial of onabotulinumtoxinA (Botox; supplied by Allergan, Irvine, CA) was reconstituted in 4 mL preservative-free saline (final concentration 25 units/mL). Injections were administered by a gynecologist using sterile technique. A sheathed 3-inch injection electromyography (EMG) needle was inserted into the vagina with digital guidance to the area of palpable muscle spasm. The needle was advanced a few millimeters through the mucosa into pelvic muscle. EMG auditory feedback was monitored by a neurologist with 30 years' experience in botulinum toxin administration to confirm placement of the needle into muscle. The toxin was injected, and the needle was then withdrawn into the sheath and placed into the next muscle for injection. The 100-unit total dose of toxin was divided among the three to four preidentified areas of muscle spasm.

Outcome measures

Prior to injection and at postinjection visits, participants were assessed for pain, muscle spasm, disability, and pain medication use. Participants completed a pain calendar for 30 days following the injection and provided a single summary rating for the month's average pain along a visual analog scale (VAS) line with endpoints of 'no pain at all' and 'worst pain imaginable'. Markings were measured and converted to an integer scale of 0–10. Pain levels at later assessments were reported by participants via marking a VAS or providing a verbal rating on a 0–10 scale. Scores of 1–3 were considered mild pain, >3 and ≤6 moderate, and >6 severe pain. Patients were also asked about onset and duration of relief from the antecedent injection. Pain medication use was tracked and recorded by the patients on their pain calendars and reviewed at each study encounter.

At in-person study visits, muscle spasm was assessed by pelvic exam with single-digit palpation of pubococcygeus, iliococcygeus, and obturator internus muscles bilaterally (figure 2). The presence and location of spasm was again recorded.

Disability was measured by the Oswestry Disability Index.[24] Disability scores of 0%–20% indicated minimal disability, 21%–40% moderate disability, 41%–60% severe disability, and 61%–80% crippled. A score over 81% indicated being bed bound or an exaggeration of symptoms.

Sample size and statistical analysis

The sample size for this study was predicated on the masked, randomized clinical trial phase. For the masked randomized portion of the protocol, it was expected that 70% of women receiving active onabotulinumtoxinA and 20% of those receiving placebo would report improvement in their pelvic pain

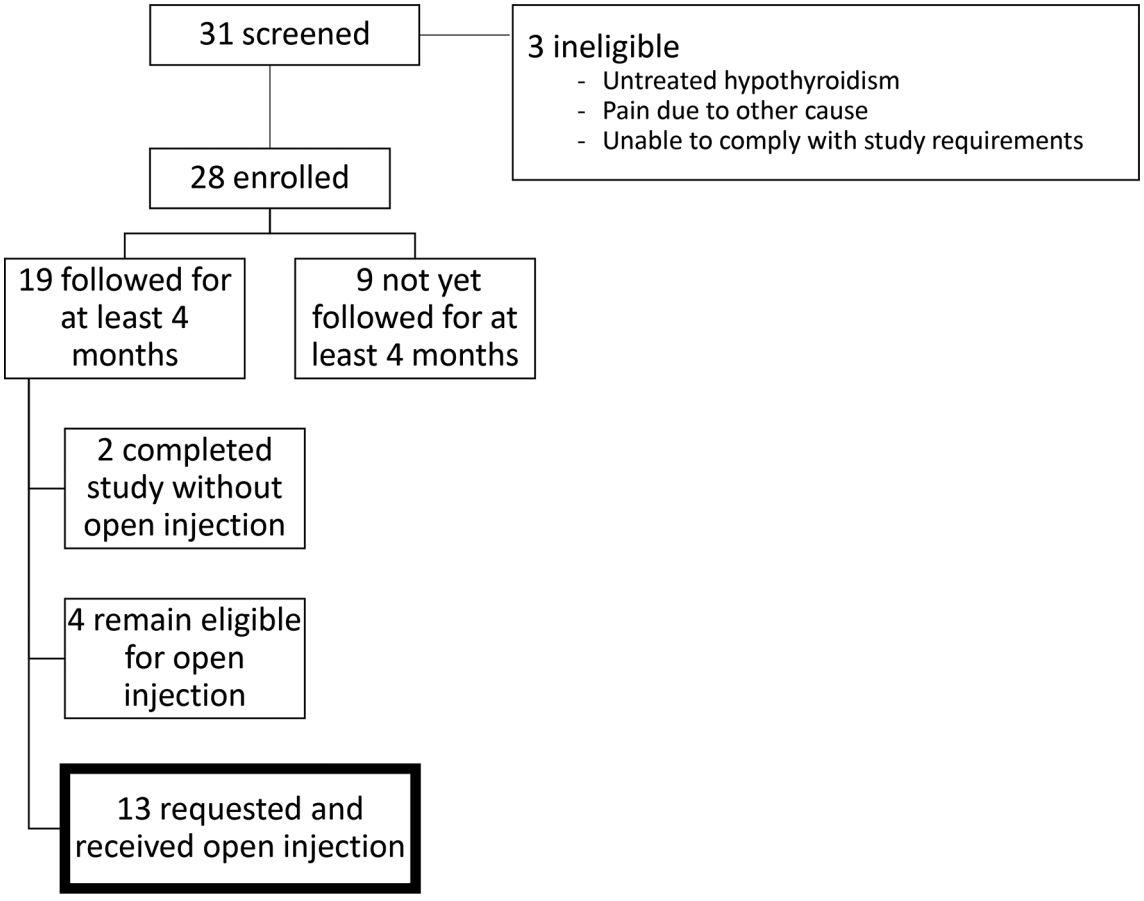

Figure 3 Consolidated Standards of Reporting Trials (CONSORT) diagram.

at 1 month, based on studies of the effectiveness of onabotulinumtoxinA for back pain.[25] The total sample size was 28, which would permit detection of benefit with 80% power using a two-tailed test of significance at $\alpha=0.05$. The interval analysis of the response to open injection data reported here was conducted when half of the targeted sample size had opted for the open injection and had been followed for at least 4 months after this injection.

Data were analyzed using SAS V.9.4 (SAS Institute), and are described as counts and percentages, or medians and ranges, as applicable. VAS scores, number of areas of spasm eliciting pain, and disability scores were compared between time points using paired t-tests or the Wilcoxon signed-rank test, as appropriate. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

As of 1 February 2018, twenty-eight women were enrolled in the randomized clinical trial. Thirteen had asked for and received the open-label onabotulinumtoxinA injection and had completed at least 4 months of follow-up. Of the other 15 participants, 2 completed the 1-year study without requesting the open onabotulinumtoxinA injection, 4 others remained eligible for but had not yet asked for the open injection, and 9 had received the open injection but had not yet completed 4 months of follow-up (figure 3). None of the 28 participants dropped out before the end of the study or had been lost to follow-up.

The participants were racially diverse and well educated (table 1). Although participants tended to be young, they reported long-standing chronic pelvic pain: a median of 7 years. All had undergone at least one surgery to diagnose and treat their endometriosis. Eight (62%) were using some form of hormonal management during research participation, most of which completely suppressed menses (table 1). The five women not using any hormonal method at the time of the study had tried hormonal therapy in the past and had found the side effects intolerable.

Pelvic floor muscle spasm on examination, required for inclusion, was identified as the primary focus of participants' endometriosis-associated pain. Of the 13 women who opted for the open-label injection, 10 requested the injection at 1 month after the randomized injection; the remaining three women requested open injection at or close to their 6-month visit. Participants were followed after the open injection for a median of 11 months (range 5–14 months), with the evaluations subsequent to the 1-month postinjection visit timed relative to the randomized injection and subject to participant availability. Complete data were available for most participants; the only information missing from analysis was the 1-month postopen injection spasm assessment for two subjects and Oswestry Disability Index for another subject.

Outcome measures

Changes in pain, spasm, and disability following the open injection are summarized in figure 4. Pain level prior to injection was moderate (median VAS score 5/10) and varied widely (preinjection VAS score range: 2–7). By 4–8 weeks after injection, all women experienced a reduction in pain (median VAS=2, range 0–5/10, $p<0.0001$), with 11 (85%) of 13 rating their pain as absent or mild (figure 4A). Seven (54%) of 13 had also reduced

Table 1 Participant demographics

Characteristic	n=13	%
Age (years)		
Median (range)	29 (21–51)	
Years of pain*		
Median (range)	7 (2–20)	
Race		
White	8	62
Black	2	15
Hispanic	2	15
Asian	1	8
Education level		
High school	2	15
College†	6	46
Graduate†	5	38
Employment status		
Student/employed	12	92
Unemployed	1	8
Hormone use		
Contraceptive pill/oral contraceptives	3	23
Intrauterine device (IUD)	4	31
IUD and contraceptive pill/oral contraceptives	1	8
None	5	38

Data are median (range) or n (%) unless indicated otherwise. Percentages may not add to 100 due to rounding.
*At study enrollment.
†Based on graduation or current enrollment.

their pain medication usage. By their final study evaluation 5–14 months later, seven women reported return of pain. Since they had experienced substantial, prolonged relief, many expressed interest in pursuing additional injections once their participation in the study was complete.

Before injection, 11 of the 13 (85%) had palpable spasm in at least four of the six assessed pelvic floor muscles (median 4 muscles, range: 1–6). On follow-up, spasm was not detectable or less widespread (≤3 muscles) in all participants (p=0.0005) (figure 4B).

Prior to injection, 5 of the 13 (38%) women were minimally disabled based on the Oswestry Disability Index. Five (38%) were moderately disabled, 2 (15%) were severely disabled, and 1 (8%) was crippled (figure 4C). Six of eight women reporting at least moderate disability (Oswestry median score: 36%, range: 22%–62%) before injection experienced improvement (Oswestry median score: 24%, range: 8%–38%, p=0.0033)

Side effects, adverse events, and concomitant treatments

The most common side effect in our cohort was temporary pain at the injection site that lasted less than 24 hours. The patients did not report injection-related urinary retention, constipation or bladder/bowel incontinence.

One patient reported an increase in back pain coincident with a decrease in her pelvic pain after injection; the back pain responded to spinal musculature botulinum toxin injections administered by her private physician. Another patient experienced increased pelvic pain 1 week after injection and new piriformis syndrome-like pain 1 month after the injection. Pelvic examination was unremarkable. Both symptoms resolved with cyclobenzaprine, removal of her progestin intrauterine device, and physical therapy. She continued menses suppression with continuous hormonal contraception to prevent dysmenorrhea. One patient experienced abdominopelvic pain after injection and increased her oral narcotic pain medication. She was subsequently hospitalized about a week after injection. On evaluation, she had constipation, and no evidence of infection or any other cause of pain. Her increased pain and constipation resolved with laxatives and decreased use of narcotics.

Some patients sought interventions for pain or gynecological issues at least 4–8 weeks after injection. One patient underwent elective hysterectomy for perimenopausal bleeding and anemia; another scheduled an elective laparoscopy for endometriosis before an anticipated lapse in her insurance benefits. One patient underwent a ketamine infusion to help with anxiety and depression.

DISCUSSION

In this open-label, proof-of-concept case series of women with surgically documented endometriosis experiencing persistent pelvic pain despite optimal hormonal and surgical treatment and who had pelvic floor spasm on examination, this spasm was found to be a significant focus of their pelvic pain, demonstrated by pain reproduction on palpation. OnabotulinumtoxinA

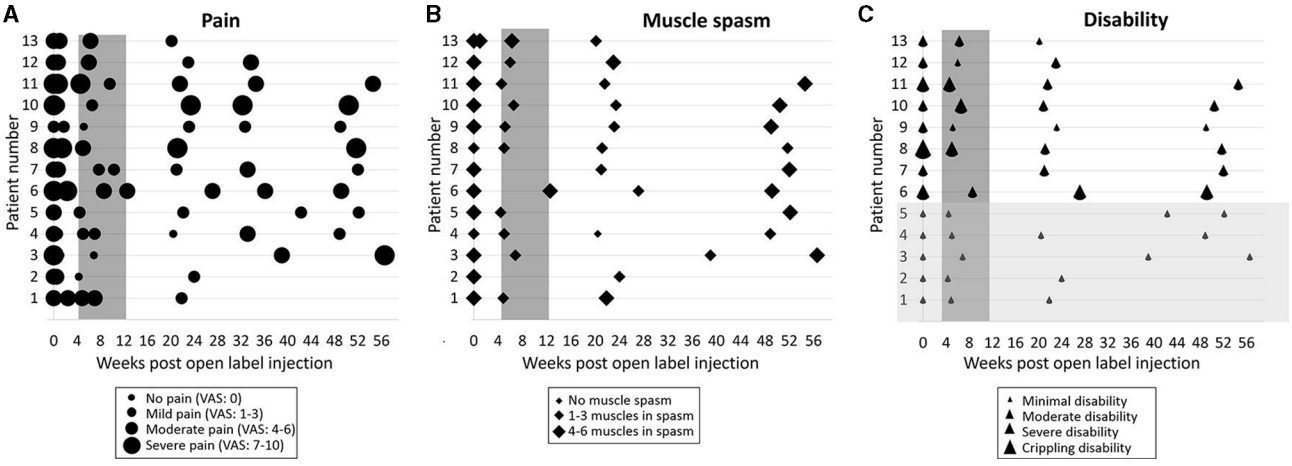

Figure 4 Changes in (A) pain, (B) muscle spasm, and (C) disability over time in weeks. Larger symbols indicate worse symptoms. Weeks 4–12, the time interval of expected maximal improvement, are shaded in dark gray. In panel (C) figure 4C, the light gray shading indicates patients with minimal preinjection disability. VAS, visual analog scale.

injection into pelvic floor muscles led to a significant reduction in both palpable muscle spasm and self-reported pain, accompanied in some patients by a reduction in the use of other pain medications. The improvement in disability in those women at least moderately disabled at baseline illustrates that this treatment can also enhance quality of life. Response was often prolonged, with some patients experiencing 6 or more months of relief. The duration of response and the temporary nature of benefit is characteristic of botulinum toxin treatment for pain. In most conditions amenable to botulinum toxin treatment, benefit can be sustained with repeated injections. Half of the 13 women included in this report expressed interest in receiving further botulinum toxin injections for pelvic pain.

Botulinum toxin is increasingly used to treat pain and appears to be especially promising in the treatment of bladder and non-bladder-related chronic pelvic pain.[21 26–28] Previous studies have not, however, focused on the efficacy of botulinum toxin for chronic pelvic pain in women with endometriosis. Our results support and extend the emerging literature on the use of botulinum toxin for chronic pelvic pain in women, which currently includes only a single, masked placebo-controlled study.[23] These prior studies did not study specific conditions known to precipitate chronic pelvic pain like endometriosis. Importantly, our study uses unique, multidimensional outcome measures that should be incorporated into future, larger intervention studies including assessment of the duration of response, concomitant medication use and the impact of treatment on disability.

Botulinum toxin offers an advantage over other approaches in that it can be safely combined with other treatment modalities and, in fact, may make patients more responsive to other pain management. For example, pelvic floor physical therapy can help manage the myofascial component of chronic pelvic pain. However, manual manipulation of the pelvic floor is often not well tolerated as it evokes extreme pain that can continue for hours after a session. If the baseline pain level and spasm can be lessened by botulinum toxin injections, physical therapy may be more easily tolerated and thus more effective at stretching and strengthening the involved muscles. Botulinum toxin also has few drug interactions and so can be used in combination with oral medications, hormones and surgery for pelvic pain.

The mechanism of botulinum toxin in treating pelvic pain likely relates directly to reduction of muscle spasm, but also probably involves direct effects on nociception. We have previously reported the presence of allodynia and hyperalgesia in women with endometriosis-related chronic pelvic pain, indicating peripheral and central sensitization.[16 29] By relieving spasm and proximal triggers for sensitization and via direct effects on peripheral and central pain pathways, botulinum toxin may also provide benefit by decreasing peripheral and/or central sensitization.

The strengths of this study lie in its stringent enrollment criteria requiring surgical documentation of endometriosis, a systematic and comprehensive data collection with very few missing data, and real-world applicability. Since concomitant treatments and therapy changes were permitted, our study shows that botulinum toxin injection can be incorporated into a comprehensive endometriosis care plan that includes a broad range of treatment modalities. By limiting enrollment to women with surgically diagnosed endometriosis, this study serves as a proof of concept for botulinum toxin injections to treat endometriosis-associated chronic pelvic pain. All patients had optimized conventional treatment prior to study enrollment, including surgical excision or ablation of endometriosis lesions. Those women who could tolerate hormone therapy used it to suppress menstruation and thus avoid dysmenorrhea, reflecting standard care of patients with endometriosis after surgery and making the study broadly generalizable. Both objective signs and patient symptoms were elicited systematically at study time points, along with prospective assessment of adverse events. The results presented here are promising and await confirmation by randomized, controlled studies which should also include similar multidimensional outcome measures.

The dose of 100 units of onabotulinumtoxinA was chosen based on the efficacy and safety of intramuscular injection of this dose in other conditions associated with excessive muscle contraction, such as spasticity and dystonia, and available vial size; however, the optimal dose for treating pelvic pain in women with endometriosis is not known. In addition, the open injections reported here were neither blinded nor placebo controlled but, rather, followed a randomized, double-blind, placebo-controlled injection in an earlier study phase by at least 1 month. Thus, we cannot assess the extent to which a placebo response, often observed in pain studies, may have been present, and, since the prior masked injection may have been toxin, the benefit observed here may reflect a cumulative effect of two injections. There was also variation in the timing of response assessment and duration of follow-up relative to the open injection, as these were predicated on the timing of the prior randomized injection and subject availability.

Our patients did not report urinary retention or incontinence. The risk of these adverse effects may have been minimized in our population as we chose a dose and dilution of toxin intended to provide injection coverage to the various affected pelvic floor muscles, divided the dose among multiple muscles to avoid a large volume of injection, and carefully monitored needle placement with EMG. Temporary and tolerable urinary retention or incontinence is not uncommon following botulinum toxin for chronic pelvic pain in women and is more likely with doses of onabotulinumtoxinA greater than 100 units.[23]

One potential confounding bias in this study is that participants were self-selected. This study cohort of women suffering with chronic endometriosis-related pain were actively searching for a non-hormonal, non-surgical, non-opioid, pain-targeted treatment to add to their current regimens. The women in our study tended to be highly educated and professionally accomplished. Importantly, despite their accomplishments, pain had a profound effect on their quality of life. The high level of their pretreatment disability illustrates a currently unmet need in developing effective pain treatments in women with endometriosis. Thus, these results are likely to be generalizable to the broader population of women with persistent endometriosis-related pelvic pain.

Other potential limitations of this study include our small sample size and our focus only on three paired muscles in the pelvic floor, since other muscles or visceral organs may also be a source of pain. In treating the pelvic floor as the only peripheral pain generator without directly addressing sensitization of the nervous system, other less prominent and perhaps previously overlooked pain generators may be unveiled. 'Viscera-visceral' hyperalgesia, in which one part of the body is sensitized to pain because of a pain generator in a spinal segmentally linked area, has been observed in rat models of other pain symptoms associated with endometriosis.[30] Each of these pain generators warrants treatment consideration, and their treatment may ultimately decrease sensitization.

In this case series, we observed a relation between pelvic muscle spasm and the patients' chronic pain such that palpation of areas of spasm recreated the pain experienced spontaneously.

As nearly half of women with endometriosis report dyspareunia as a pain symptom, vaginismus and spasm in pelvic floor muscles may be an expected finding.[1 31] It remains to be determined whether pelvic floor muscle spasm is present in all women with persistent endometriosis-associated chronic pelvic pain.

Examination for pelvic muscle spasm and for evidence of peripheral and central sensitization will help further delineate the phenotype of this disorder. This study provides preliminary evidence that in women with evidence of pain arising from pelvic floor muscles, this approach might best be considered after the visceral aspects driving their pain have been managed, possibly with suppression of menses, and optimization of bowel and bladder function. Importantly, this procedure may offer an opportunity to reduce opioid use. This intervention may then be incorporated into the chronic pain model of care, enabling a precision medicine approach with individualized, multifaceted treatment.

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Competing interests BIK is also an investigator on one study for which the NIH has received a grant from Allergan and another study for which the NIH has received a grant from Merz.

Patient consent for publication Not required.

Ethics approval The clinical trial (NCT identifier: NCT01553201) was approved by the Institutional Review Board of the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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