Botulinum Toxin Type A for Chronic Pain and Pelvic Floor Spasm in Women

A Randomized Controlled Trial

Jason A. Abbott, PhD, FRANZCOG, Sherin K. Jarvis, BAppSc(Physio), Stephen D. Lyons, PhD, MRANZCOG, Angus Thomson, MRCOG, and Thierry G. Vancaille, MD, FRANZCOG

OBJECTIVE: To estimate whether botulinum toxin type A is more effective than placebo at reducing pain and pelvic floor pressure in women with chronic pelvic pain and pelvic floor muscle spasm.

METHODS: This study was a double-blinded, randomized, placebo-controlled trial. All participants presented with chronic pelvic pain of more than 2 years duration and evidence of pelvic floor muscle spasm. Thirty women had 80 units of botulinum toxin type A injected into the pelvic floor muscles, and 30 women received saline. Dysmenorrhea, dyspareunia, dyschezia, and nonmenstrual pelvic pain were assessed by visual analog scale (VAS) at baseline and then monthly for 6 months. Pelvic floor pressures were measured by vaginal manometry.

RESULTS: There was significant change from baseline in the botulinum toxin type A group for dyspareunia (VAS score 66 versus 12; χ^2=25.78, P<.001) and nonmenstrual pelvic pain (VAS score 51 versus 22; χ^2=16.98, P=.009). In the placebo group only dyspareunia was significantly reduced from baseline (64 versus 27; χ^2=2.98, P=.043). There was a significant reduction in pelvic floor pressure (centimeters of H_2O) in the botulinum toxin type A group from baseline (49 versus 32; χ^2=39.53, P<.001), with the placebo group also having lower pelvic floor muscle pressures (44 versus 39; χ^2=19.85, P=.003).

CONCLUSION: Objective reduction of pelvic floor spasm reduces some types of pelvic pain. Botulinum toxin type A reduces pressure in the pelvic floor muscles more than placebo. Botulinum toxin type A may be a useful agent in women with pelvic floor muscle spasm and chronic pelvic pain who do not respond to conservative physical therapy.

CLINICAL TRIAL REGISTRATION: Australian Clinical Trials Registry, http://www.actr.org.au/, ACTRN012605000515695

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LEVEL OF EVIDENCE: I

Chronic pelvic pain in women causes morbidity for the sufferer and incurs high cost for health care providers.[1] There are frequently problems with diagnosis and management of what is commonly a relapsing and debilitating health issue for women. Although many causes of female pelvic pain are effectively treated by existing medical and surgical interventions, there remains a group of women for whom chronic pelvic pain is either undiagnosed or ineffectively treated.[2]

Pain due to muscle spasm is reported to occur in the head,[3] back,[4] and neck,[5] and treatments aimed at reducing the muscle spasm are able to reduce pain.[6] In a pilot study of women with chronic pelvic pain and demonstrable spasm in the pelvic floor muscles, we found a universal reduction in pressure when botulinum toxin type A (BOTOX, Allergan Westport, Ireland) was injected, and many women reported diminution of pain symptoms.[7] The aim of the current study is to report change in pelvic floor pressure, pain response, and impact on quality of life when women with chronic pelvic pain and pelvic floor muscle spasm are randomized to receive botulinum toxin

From the University of New South Wales, Sydney Australia; Department of Endo-Gynaecology, Royal Hospital for Women, Sydney Australia; and Worcestershire Acute Hospitals Trust, Worcester, United Kingdom.

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Corresponding author: Jason Abbott, Department of Endo-Gynaecology, Royal Hospital for Women, Barker Street Randwick 2031, Sydney, Australia; e-mail: jason.abbott@sesiahs.health.nsw.gov.au or stephen.lyons@sesiahs.health.nsw.gov.au.

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type A or placebo injections to the pelvic floor muscles.

MATERIALS AND METHODS

This study received approval from the institutional scientific and ethics committees. Study participants signed informed consent after receiving written information and having the opportunity to ask research staff study-related questions. Between January 2004 and November 2004, 401 responders to a media release were screened by telephone as to their possible suitability for the study. Women who lived outside of the Sydney metropolitan area, who had pain other than female pelvic pain, or who had known untreated endometriosis were excluded from further participation.

Suitable participants in the study were women aged 18–55 years who had more than 2 years of chronic pelvic pain that caused disruption to their daily activities. Participants were required to have objective evidence of *pelvic floor myalgia*, defined as the presence of contracted, painful muscles on palpation and elevated resting pressures (more than 40 cm H_2O) by vaginal manometry. Women were not required to have had standard physical therapy for pelvic pain before inclusion. Women had to be willing to attend the clinic for eight visits over 6 months following study treatment. Figure 1 reports patient disposition through the study. The primary reason for noninclusion was an inability to demonstrate pelvic floor spasm. Eight women were found to meet all entry criteria but declined further participation in the study.

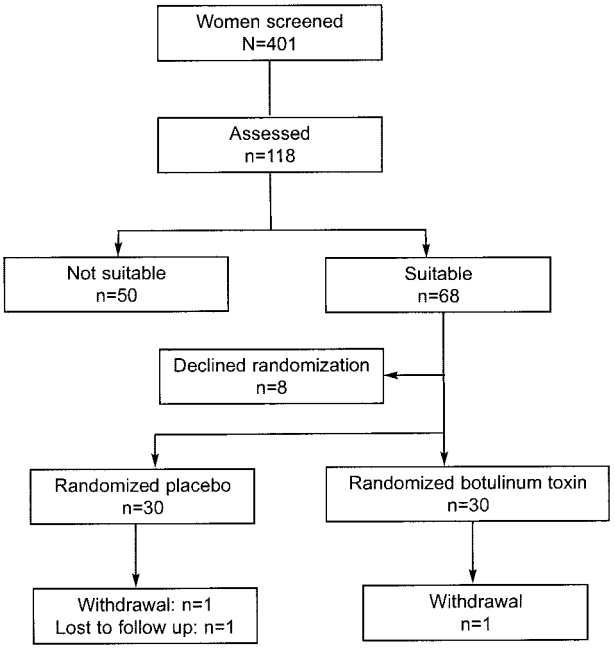

Fig. 1. Patient disposition throughout the study.
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Women were excluded if they were breastfeeding, pregnant, or desiring pregnancy during the study period, were unwilling to use contraception during the study period, or had previously received botulinum toxin type A injections to the pelvic floor. Palpable pelvic pathology, current use of aminoglycoside antibiotics, history of neurologic or bleeding disorders, and known sensitivity to the formulation of botulinum toxin type A were also reasons for exclusion.

Participating women were asked to complete demographic data and undergo a full medical history and detailed examination. Women suppressing menstruation with the oral contraceptive pill or progesterone were asked to continue with these medications. A record of change in medication was taken at each visit. Assessment of pain was performed by visual analog scale (VAS), with separate scores obtained for dysmenorrhea, dyspareunia, dyschezia, and nonmenstrual pelvic pain. Quality of life data were collected by three separate and validated instruments: the EuroQOL-5D (EQ-5D) measures function over five dimensions and a self-rated assessment of health,[8] the Short Form 12 Health Survey (SF-12) produces scores for physical and mental health,[9] and the Sexual Activity Questionnaire scores sexual function in relation to pleasure, discomfort, and habit.[10] Questionnaires for bladder[11] and bowel function[12] were also completed and uroflowmetry performed.

On the day of injection, women fasted for 6 hours before their scheduled injection and had a urinary pregnancy test performed if they had not had a hysterectomy. Vaginal manometry was performed via an air-filled vaginal probe (Peritron; Cardio Design, Melbourne, Australia). Recorded assessments included resting pressure and maximum contraction pressure.

Women were randomized to receive either 80 units of botulinum toxin type A at a concentration of 20 units/mL or saline injections (placebo group), using computer-generated randomization sequences in balanced blocks of 20. No stratification was undertaken. Central telephone randomization was performed after patient details were entered into a password-protected database by a certified research administrator not involved in clinical care. Dispensing of medication followed a standardized protocol, with two registered nurses who were not involved in

any other area of the study checking and preparing the medications for injection. Medications were delivered to the administering doctor in identical, sterile, puncture-proof containers with the solution for injection drawn up in four identical 1-mL syringes with 22G Yale spinal needles attached.

The injection procedure has been previously described in detail[7] and is summarized here. Under conscious sedation monitored by an anesthetist, the pelvic floor muscles were examined vaginally and 1-mL aliquots of the study drug injected into two sites bilaterally within each of the puborectalis and pubococcygeus muscles. Women recovered for 1–2 hours until they could eat, drink, mobilize, and void. Follow-up occurred by telephone 2–3 days after injection, and then reviews were performed at 2, 4, 8, 12, 16, 20, and 26 weeks after injection. At these follow-up times, study participants completed VAS scores for pain, bowel, and bladder questionnaires and had examinations to assess pelvic floor tenderness, vaginal manometry measurements, and other physical findings at bimanual examination. Quality-of-life and sexual activity questionnaires were administered at weeks 4, 12, and 26 after injection.

Sample size for this trial was calculated based on the results of the pilot study data that demonstrated a mean reduction in pain of 50% on VAS scores and improvements in all aspects of quality of life. Given that 75% of women reported pain reduction in this study and estimating a 30% placebo effect, to find a clinically significant difference of 50% between the two groups with a power of 80%, 60 women are required, with 30 randomized to each of botulinum toxin type A and placebo groups.

Group histograms of variables for analysis were tested to ascertain distribution and subjected to Levene's test for normality. Intergroup analyses for independent parametric data were assessed using the Student *t* test or the Mann-Whitney *U* test for its nonparametric equivalent. Intragroup comparisons were assessed using the Freidman test for multiple, dependent nonparametric data. Dichotomous data were compared using χ^2 analysis and Fisher exact test, as appropriate, to sample size. Probability values are two-tailed, and significance is set at $P<.05$. All analyses are by intention to treat. Statistical analyses were performed with SPSS 13.0 (SPSS Inc, Chicago, IL).

Data audit was performed at study completion by selecting a 10% random sample of case report forms and checking for completeness and correct data entry. Error and omission rate was less than 0.015% by this method. Critical entry fields were fully audited by two authors for completeness and correctness of entry.

RESULTS

The demography and history of the groups were similar as noted in Table 1. There were no statistically significant differences in these data. Only two (6%) women in the botulinum toxin type A group and three (10%) women in the placebo group had not previously undergone a surgical procedure. Endometriosis was the most common previous diagnosis, with 33 of 60 (55%) women having histologically confirmed disease. Seven (11%) women had a previous negative laparoscopy, four had a diagnosis of adhesions, two had an ovarian cyst, and one had no pathology noted. One woman each reported previous ectopic pregnancy, Asherman syndrome, endosalpingiosis, and hysterectomy, and five women did not know the pathology of their previous surgeries.

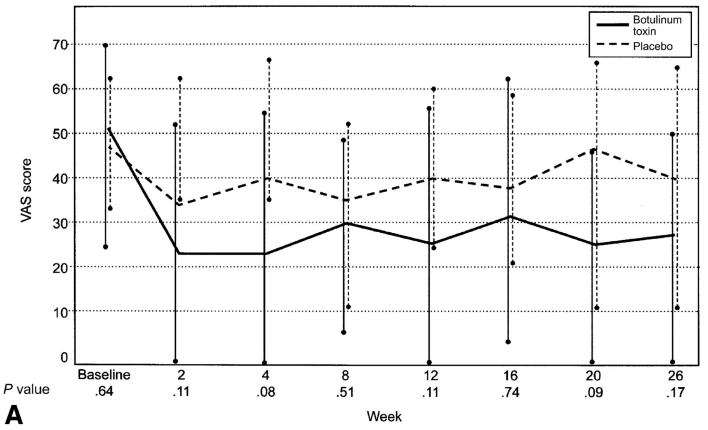
The pain scores for different types of pain assessed in the study are shown in Figure 2. Pain scores were reduced for both groups in all parameters, but there were no statistically significant intergroup differences. For intragroup differences, nonmenstrual pelvic pain is found to be significantly different from baseline in the botulinum toxin type A group (VAS score 51 versus 22; $\chi^2=16.98$, $P=.009$), as is dyspareunia (VAS score 66 versus 12; $\chi^2=25.78$, $P<.001$). In the placebo group, only dyspareunia is significantly reduced from baseline (64 versus 27; $\chi^2=2.98$, $P=.043$).

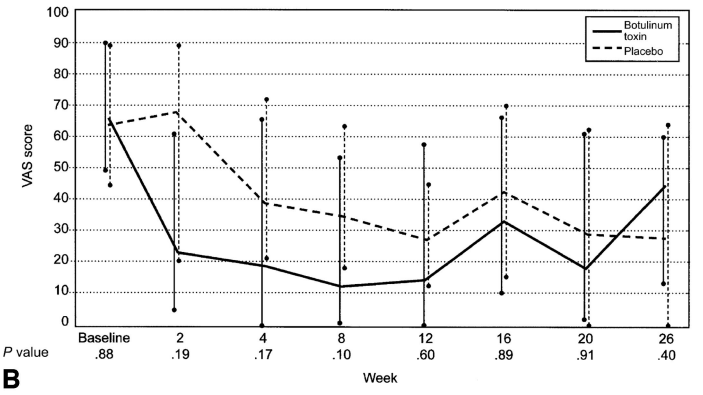
Figure 3 summarizes intergroup comparisons of resting and maximum pelvic floor pressures throughout the course of the study. Intragroup analysis in the botulinum toxin type A group shows a highly significant reduction in resting pelvic floor pressure from baseline (49 versus 32; $\chi^2=39.53$, $P<.001$), with the

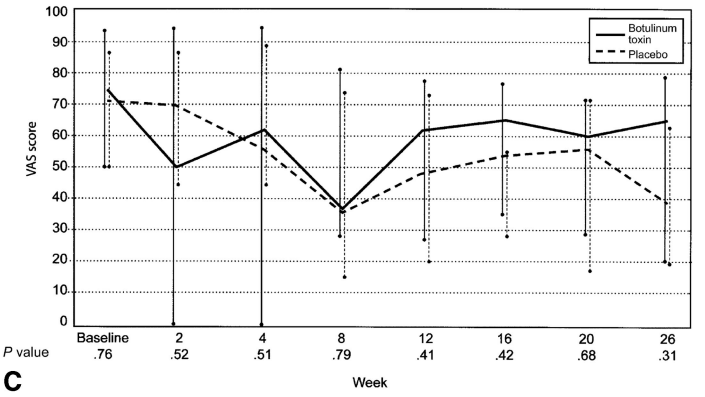
Table 1. Patient Demographics

Parameter	BOTOX (n=30)	Placebo (n=30)
Age (y, mean±standard deviation)	30.6±8.1	30.5±7.5
Ethnicity: white	27 (90)	27 (90)
In current relationship	17 (56)	15 (50)
Smokers	12 (40)	12 (40)
University graduates	10 (33)	14 (47)
Exercise regularly	20 (67)	22 (73)
Previous delivery	8 (27)	6 (20)
Previous history sexual abuse	9 (30)	6 (20)
Previous abdominal surgery	28 (93)	27 (90)
Previous laparoscopy	26 (87)	27 (90)
Median number laparoscopy (range)	2 (0–10)	2 (0–10)

BOTOX, botulinum toxin type A.
Data are expressed as n (%) except where otherwise indicated.







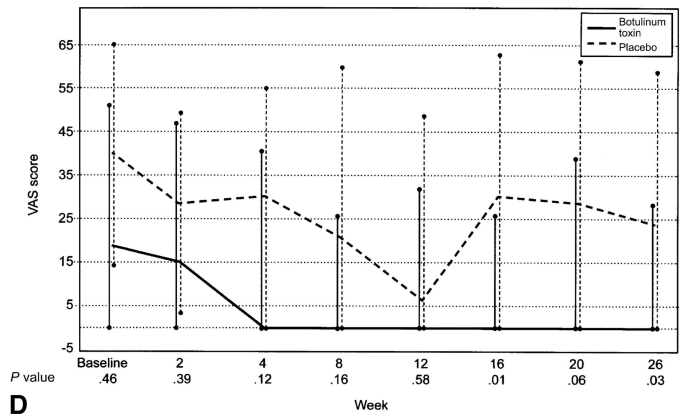


Fig. 2. Pain scores throughout the study. **A.** Nonmenstrual pelvic pain. **B.** Dyspareunia. **C.** Dysmenorrhea. **D.** Dyschezia. Horizontal lines represent median scores, and vertical lines represent interquartile ranges.

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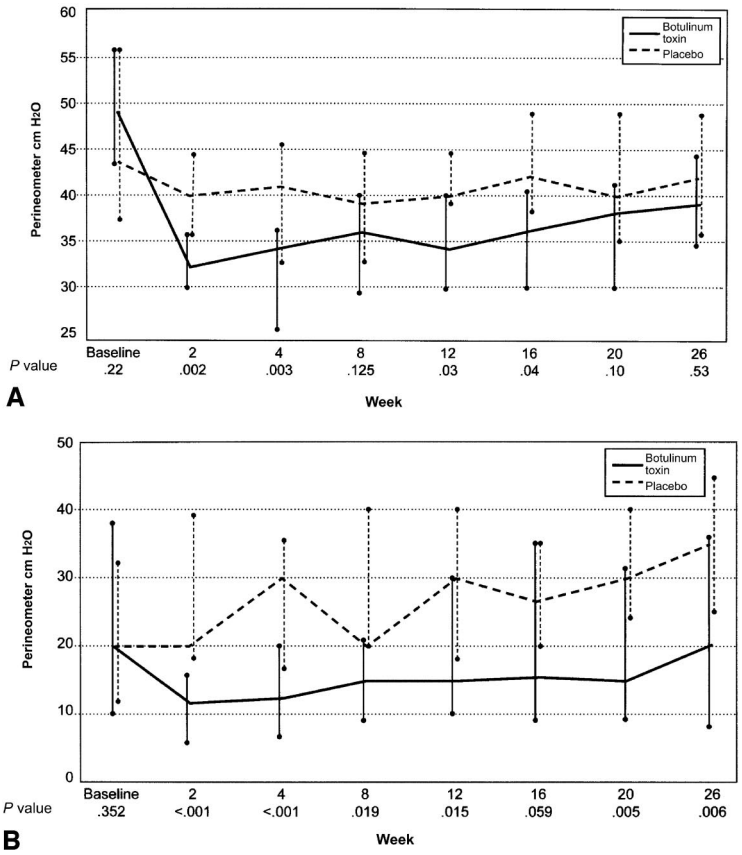

Fig. 3. Pressure scores throughout the study. **A.** Resting pressure. **B.** Maximum contraction pressure. Horizontal lines represent median scores, and vertical lines represent interquartile ranges.

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placebo group also having lower resting pressures (44 versus 39; $\chi^2=19.85$, $P=.003$).

Table 2 compares quality of life data throughout the study. Outcomes from these instruments show improvement in both groups throughout the 6 months of study, with women in the botulinum toxin type A group generally reporting better quality of life, although this did not reach statistical significance.

For independent uroflowmetry, there was no difference between the groups at baseline, or when assessed at 4, 12, 16, or 20 weeks after injection for total urinary volume, maximal flow rate, average flow rate, or residual urinary volume. There was no difference between the groups in the overall scores for the bladder function questionnaire at baseline (botulinum toxin type A 6.13 versus placebo 6.17; $Z=-0.853$, $P=.394$) or subsequent assessments. There was no difference between the groups in the overall scores for the bowel function questionnaire at baseline (botulinum toxin type A 1.53 versus placebo 1.07; $Z=-0.146$, $P=.884$) or at subsequent assessments.

There were two women who became pregnant during the study, both in the botulinum toxin type A group, at 4 months and 5 months following injection. One woman spontaneously delivered a live female infant with no neonatal abnormalities. The other was a 41-year-old primigravida with a longstanding history of endometriosis, vulvodynia, and primary infertility with previously documented tubal damage and occlusion. She had an elective cesarean delivery at 40 weeks. Her infant has a ventriculo-septal defect that will require surgical correction.

Two women in the placebo group requested laparoscopy for severe ongoing pain during the study period. Both had histories of endometriosis. One had no macroscopic or microscopic evidence of disease; the second woman, who had previously undergone hysterectomy, had histologically confirmed residual endometriosis in the vaginal vault that required surgical resection.

During the injection procedure, the main complication was of vaginal bleeding from the injection sites, which was controlled by digital pressure followed by insertion of a medium dilator. There were no anesthetic complications. During the follow-up period, 123 adverse events were reported in the botulinum toxin type A group and 134 in the placebo group ($\chi^2=0.349$,

Table 2. Quality of Life Data

	Baseline	4 Weeks	12 Weeks	16 Weeks	20 Weeks	26 Weeks	Intragroup Comparison*
EQ-5D index							
BOTOX	0.62 (0.16–0.73)	0.75 (0.69–0.81)	0.73 (0.41–0.85)	0.80 (0.61–0.80)	0.73 (0.69–0.80)	0.78 (0.69–1.00)	χ^2=12.6, *P*=.02
Placebo	0.65 (0.23–0.70)	0.69 (0.62–0.76)	0.71 (0.62–0.80)	0.73 (0.62–0.79)	0.69 (0.18–0.83)	0.69 (0.25–0.81)	χ^2=15.1, *P*=.01
BOTOX versus placebo†	Z=−.24, *P*=.82	Z=−1.99, *P*=.04	Z=−.24, *P*=.81	Z=−.92, *P*=.36	Z=−1.16, *P*=.24	Z=−2.12, *P*=.03	
EQ-5D VAS score							
BOTOX	52 (49–70)	80 (58–90)	70 (60–85)	70 (52–82)	71 (60–80)	70 (51–80)	χ^2=13.7, *P*=.01
Placebo	51 (45–66)	60 (40–80)	61 (58–76)	70 (52–80)	70 (55–80)	70 (40–80)	χ^2=8.2, *P*=.14
BOTOX versus placebo†	Z=−29, *P*=.77	Z=−2.19, *P*=.02	Z=−1.31, *P*=.19	Z=−.39, *P*=.69	Z=−.71, *P*=.47	Z=−.42, *P*=.67	
SF-12 Physical component score							
BOTOX	38.44 (31.65–46.64)	41.03 (34.07–51.79)	43.94 (33.44–54.09)	43.26 (32.81–54.14)	48.89 (34.16–54.16)	46.20 (37.55–54.09)	χ^2=4.39, *P*=.49
Placebo	37.19 (30.21–40.59)	41.20 (33.35–44.65)	38.00 (32.66–45.34)	43.80 (32.84–49.60)	44.26 (27.17–52.58)	44.83 (37.08–54.16)	χ^2=12.32, *P*=.03
BOTOX versus placebo†	Z=−.77, *P*=.47	Z=−1.43, *P*=.15	Z=−1.45, *P*=.14	Z=−.35, *P*=.72	Z=−.35, *P*=.17	Z=−.50, *P*=.62	
SF-12 Mental component score							
BOTOX	41.03 (34.02–53.02)	45.95 (37.75–56.08)	45.30 (37.87–55.35)	47.66 (38.03–57.83)	48.27 (36.87–56.62)	49.75 (36.77–56.45)	χ^2=1.32, *P*=.93
Placebo	42.08 (33.44–51.77)	48.91 (32.88–55.71)	46.06 (36.91–55.20)	43.84 (32.42–50.94)	43.04 (31.64–51.92)	44.88 (30.46–56.67)	χ^2=7.1, *P*=.21
BOTOX versus placebo†	Z=0, *P*=1.0	Z=−.13, *P*=.89	Z=−.06, *P*=.94	Z=−1.33, *P*=.18	Z=−1.58, *P*=.11	Z=−.88, *P*=.37	
Pleasure (Higher score= more sexual pleasure)							
BOTOX	9 (5.5–13)	12 (9–13.5)	11 (8–15)	11 (8–15)	11 (6.2–13)	11.5 (7.2–13.7)	χ^2=4.02, *P*=.54
Placebo	8 (7–11)	10 (7.5–12)	10.5 (8–13)	10.5 (8–13)	10.5 (9–12)	10 (8.5–13)	χ^2=3.07, *P*=.68
BOTOX versus placebo†	Z=−0.07, *P*=.94	Z=−1.59, *P*=.11	Z=−0.51, *P*=.61	Z=−0.51, *P*=.63	Z=−0.04, *P*=.96	Z=−0.64, *P*=.52	
Habit (Higher score=greater frequency of intercourse)							
BOTOX	1 (0–1)	1 (0–1.5)	1 (1–1.5)	1 (0–1.5)	1 (0–1)	1 (1–1.75)	χ^2=6.21, *P*=.28
Placebo	1 (0–1)	1 (0–1.5)	1 (0–1)	1 (0–1)	1 (0–1.2)	1 (0–1)	χ^2=1.05, *P*=.95
BOTOX versus placebo†	Z=−0.77, *P*=.49	Z=−.27, *P*=.83	Z=−0.67, *P*=.49	Z=−0.63, *P*=.49	Z=−0.22, *P*=.82	Z=−2.2, *P*=.025	
Discomfort (Higher score= more pain)							
BOTOX	3 (2.5–4.5)	2 (1–3.5)	3 (1–4)	3 (1–4)	1.5 (1–3.7)	2 (1–4)	χ^2=5.77, *P*=.32
Placebo	5 (3–6)	2.5 (1.75–4)	3.5 (2–4)	3.5 (2–4)	3 (1–4)	2 (1–4)	χ^2=9.71, *P*=.08
BOTOX versus placebo†	Z=−1.58, *P*=.11	Z=−1.23, *P*=.22	Z=−1.19, *P*=.23	Z=−1.19, *P*=.23	Z=−1.01, *P*=.31	Z=−0.27, *P*=.78	

EQ-5D, EuroQOL-5D; BOTOX, botulinum toxin type A; VAS, visual analog scale; SF-12, Short Form-12 Health Survey.
Data are expressed as median (interquartile range).
* Freidman test.
† Mann-Whitney *U* test.

P=.555). These were classified as cold/flu-like illness (botulinum toxin type A versus placebo; 33 versus 42 events; χ^2=1.280, P=.258), gastroenterological (11 versus 8 events; χ^2=0.370, P=.583), headache/neurological (20 versus 20 events; χ^2=0 P=1), pelvic/back pain (26 versus 30 events; χ^2=0.323, P=.570), and nonstudy-related or other nonsignificant events (25 versus 29 events; χ^2=0.334, P=.563).

Notable events and serious complications occurred in four women in the botulinum toxin type A group, two of whom became pregnant during the study period, one of whom had urinary stress incontinence on several occasions, and one of whom had urge and stress urinary incontinence, flatus, and fecal incontinence intermittently for 4 months. No woman in the placebo group had a serious or notable complication. There was no difference in the number of women with incontinence (fecal or urinary) between the groups (P=.492, Fisher exact test).

DISCUSSION

The use of botulinum toxin type A, which blocks cholinergic transmission at the neuromuscular junction, is reported to decrease pain and improve function in cervical dystonia,[5] limb spasticity after cerebrovascular accident[13] and headache.[3] Our group has previously recognized and reported on levator spasm and treatment with botulinum toxin type A for chronic pelvic pain in women.[7] In this double-blind, placebo-controlled study significant intergroup differences for individual pain scores were not demonstrated. There are a number of factors that may contribute to the reporting of reduced pain in the placebo group. The placebo response is recognized as contributory to an improvement in clinical outcomes, and complex neurobiological,[14] psychological,[15,16] and social factors[17] are implicated. Regression to the mean for a dynamic, subjective variable such as pain may have occurred after the concealed intervention. Patient uncertainty has been previously reported to cause more conservative estimates of pain perception.[18]

Muscle needling (without injection) is reported to decrease muscle spasm–an effect commonly associated with acupuncture.[19] In addition, desensitizing trigger points is demonstrated to relieve muscle spasm and pain.[20] The repeated measurement of pelvic floor pressures by perineometry using a relax/contract model is standard physical therapy for pelvic floor spasm in our department. Women in the placebo group who had not been through this program may have used this approach as a means of reducing pain, similar to that reported in chronic pelvic pain in men.[21] Finally, the effect of psychotherapy should not be underestimated because a significant proportion of the women in this study have a history of sexual abuse, which is reported to be a common finding in women with pelvic pain.[22] The frequent postinjection consultation with assessment, discussion, and personal attention by a small research team may have contributed to the perception of reduced pain and a lesser degree of discomfort during physical examination.[23]

Because the response in the placebo group was greater than that estimated in the power calculation, it is possible that a type II error has occurred. A larger sample size or the addition of a nocebo group may have demonstrated a significant difference.

Women in the botulinum toxin type A group had significantly less nonmenstrual pelvic pain following injection. Because many women were not sexually active or menstruating and few had dyschezia at baseline, this symptom is often the primary or only pain present. Causes for this greater pain reduction due to botulinum toxin type A injection may include chemodenervation at the neuromuscular junction,[24] inhibition of γ motor endings in muscle spindles that leads to muscle atrophy and prolongation of the analgesic effect beyond the duration of activity of the toxin on the motor end plate,[25] and possibly by other effects on the central nervous system and as yet unrealized actions.[26]

Pelvic floor pressure measurement by perineometry is both acceptable and has high validity.[27] There was a clear advantage with botulinum toxin type A injection compared with normal saline for reducing pelvic floor muscle spasm measured by this technique. Because botulinum toxin type A is not injected into all pelvic floor muscles, complete paralysis is not achieved as noted in the ability of patients to generate some, albeit considerably reduced, contraction of the pelvic floor. This may be a factor if there is nonresponse or incomplete response to the injection. A potential criticism of this study may be that electromyogram equipment was not used to assess needle placement in muscles, but clinically in this study maximum contraction pressure was markedly reduced in the botulinum toxin type A group and was increased in the placebo group, thus demonstrating appropriate and accurate placement of the toxin.

This study differs from the use of botulinum toxin type A in other areas of the body where muscle spasm appears to be primary (such as blepharospasm, torticollis, and cervical dystonia) or related to a neurological problem (cerebral palsy, cerebrovascular accident). The majority of patients in this study had surgical intervention for diagnosis and treatment of their chronic pelvic

pain, with a majority having endometriosis. In such cases, pelvic floor myalgia appears to be secondary and independent of the normal neuromuscular controls. Recognition that pelvic floor spasm may contribute to ongoing pain symptoms offers some explanation as to why conventional medical and surgical treatments may be ineffective for endometriosis and other organic diseases of the female pelvis. It also presents a new avenue for the management of chronic pelvic pain in the face of previous failed treatments for these women. Recurrence of symptoms after treatment of both the pathology and the myalgia may be a harbinger of primary disease recurrence, which is not uncommon[28] and was reported in this study. Like elsewhere in the body, primary pelvic floor myalgia may also occur, and it is unclear at this time whether this offers an improved outcome for patients, with reduced need for reinjection of botulinum toxin type A, should initial therapy be successful.[29]

It is important to note that women in the botulinum toxin type A group did not suffer an increase in adverse events compared with those receiving saline injections, although there does appear to be a transient and mild effect on pelvic sphincters. Such information is important in counseling patients and obtaining consent for this procedure.

An improvement in all measures of quality of life was demonstrated, with botulinum toxin type A producing greater benefit compared with placebo for nearly all parameters. Although there were some statistically significant differences at individual evaluation points, caution should be undertaken because the numbers are relatively small. Further study in this area may be directed toward developing more specific quality-of-life instruments for assessment.

This randomized, placebo-controlled trial reports that pelvic floor spasm can cause pain, with improvement in some pain symptoms occurring by reducing muscle spasm. Although there were no significant intergroup differences demonstrated in this study between botulinum toxin type A and placebo for pain scores, the study has demonstrated that elevated pelvic floor tone contributes to pelvic pain and that botulinum toxin type A has clear advantages over placebo in reducing pelvic floor spasm. The importance of physical therapy is recognized and recommended as first-line therapy for women with chronic pelvic pain due to pelvic floor myalgia. For women who are unresponsive to conservative treatment, botulinum toxin type A is an effective treatment for reducing pelvic floor pressure and associated pain symptoms, with an acceptable adverse-effect profile. Ongoing research in this area is essential to further define this new tool in the treatment of a debilitating condition in women.

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