Original Research

Botulinum Toxin A as a Treatment for Provoked Vestibulodynia

A Randomized Controlled Trial

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OBJECTIVE: To evaluate pain reduction after two injections of 50 units botulinum toxin A compared with placebo for provoked vestibulodynia.

METHODS: We conducted a double-blinded, placebo-controlled randomized trial of 50 units botulinum toxin A or placebo injected in the bulbocavernosus muscles twice, 3 months apart, in women with provoked vestibulodynia. Primary outcome was self-reported dyspareunia or pain at tampon use on a visual analog scale (VAS, 0–100). Secondary outcomes were pain at weekly tampon insertion (VAS score), reduction of pelvic floor hypertonicity (measured with a vaginal manometer), adverse events, and sexual function and distress. A sample size of 38 participants for each group was calculated to achieve a statistical power of 80% based on an effect size of 20 VAS units (0–100) (mean score range 56–76±31 SD).

RESULTS: Between May 2016 and June 2018, 124 women with provoked vestibulodynia were assessed, and 88 were randomized to botulinum toxin A (BTA group, n=44) or placebo (placebo group, n=44). Primary outcome showed a lower but statistically nonsignificant pain rating by 7 VAS units (95% CI −15.0 to 0.4) in the BTA group compared with the placebo group. Secondary results showed a significant decrease in pain at weekly tampon insertion by 11 VAS units (95% CI −16.6 to 6.0) with botulinum toxin A injection. The vaginal manometer measured lower maximum contraction strength by 7 mm Hg (95% CI −12.7 to −2.4) and lower 10-second endurance strength by 4 mm Hg (95% CI −7.72 to −1.16) in the BTA group compared with the placebo group. No changes were observed for sexual function and distress, but there was a significant increase in women attempting vaginal intercourse in the BTA group (0.27, 95% CI 0.06–0.48). No severe adverse events were reported.

CONCLUSION: Twice-repeated injections of 50 units of botulinum toxin A in women with provoked vestibulodynia did not reduce dyspareunia or pain at tampon use, but secondary outcomes suggested positive effects of the treatment.

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Vulvodynia is a common pain disorder among premenopausal women, with an estimated prevalence of 10–15%. The most common subtype is provoked vestibulodynia, which is characterized by severe pain on touch or pressure of the mucosa around the vaginal opening.[1–3] The pain and its associated sexual consequences have a severe negative effect on the quality of life of affected individuals.[4,5]

The etiology of provoked vestibulodynia is unclear, but there is evidence of pathophysiologic changes in three interdependent systems: neurogenic inflammation[6–8] with sensitization in the vestibular tissue, hyperactivity in the pelvic floor muscles,[9–11] and changes in the pain regulatory pathways of the central nervous system.[4] Evidence suggests that the

hyperactivity in the pelvic floor muscles exacerbates and maintains the neurogenic inflammation and pain.[12]

Physical therapy is usually the first-line treatment for pelvic floor muscle hyperactivity, but treatment with botulinum toxin A injections in certain pelvic floor muscles is used increasingly, although it has been tested to only a limited extent.[13,14] Published reports on the effect of botulinum toxin A on provoked vestibulodynia are few, and methods of injection, doses, and evaluation of treatment effect differ.[15–17] At the time of initiating our study, only one double-blind randomized controlled trial had been published, in which a single treatment with 20 units of botulinum toxin A in the bulbocavernosus muscles showed no additional effect of botulinum toxin A compared with saline.[15]

We, therefore, hypothesized that two injections with a 3-month interval of 50 units of botulinum toxin A in the bulbocavernosus muscles in women with provoked vestibulodynia would decrease pain during intercourse or tampon insertion and would reduce muscular hyperactivity.

METHODS

Eighty-eight women with provoked vestibulodynia were included in the study. They were recruited between May 2016 and June 2018 from the outpatient vulvar clinic at Danderyd Hospital, Stockholm, by advertising on social media and by referrals from other outpatient gynecologic clinics in the Stockholm region. Study approval was obtained from the Ethical Review Board in Stockholm, and approval for off-label use of Botox (botulinum toxin A) was obtained from the Swedish Medical Products Agency. The study is registered at ClinicalTrials.gov (www.clinicaltrials.gov,NCT02773641) and at eudract.ema.europa.eu/, with EudraCT number 2016-000375-25. The participants received written and verbal information and signed a consent form. The study was performed at the Department of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, and conducted according to Good Clinical Practice and monitored by the department's Good Clinical Practice unit.

The study was a double-blind randomized placebo-controlled trial of either active treatment with 50 units of botulinum toxin A (BTA group; Allergan) or placebo (placebo group) injected bilaterally in the bulbocavernosus muscles, repeated twice. Study participants as well as care givers were blinded to the treatment. Treatment interval was 3 months. Inclusion criteria were age 18–40 years, nulliparous, at least 3 months of pain on touch around the vaginal opening, painful coitus or tampon insertion reported as 60 or higher on a visual analog scale (VAS, 0–100), and heightened tonicity in the bulbocavernosus muscles on digital palpation. Exclusion criteria were local infection, dermatologic disease or other causes for coital pain, severe psychiatric or somatic disease, contraindication to botulinum toxin A (peripheral motor neuron disease such as myasthenia gravis, amyotrophic lateral sclerosis, Lambert-Eaton syndrome, and diabetes), daily use of pain medication, pregnancy, and urinary or flatulence incontinence.

The primary outcome was the reduction in patient self-reported dyspareunia or pain at tampon use during the previous month using a VAS of 0 (no pain) to 100 (worst pain imaginable). Secondary outcomes included pain evoked by weekly tampon insertion at home, reported on a VAS (0–100), to assess the onset and duration of a possible effect of botulinum toxin A injections, reduction of pelvic floor hyperactivity and tonus measured with a vaginal manometer, effect on sexual function, and monitoring of possible botulinum toxin A–related adverse events.

A total of five research appointments were planned. An overview of the visits can be seen in Box 1. At visit 1 (baseline), the patients were first screened for inclusion and exclusion criteria by filling out a questionnaire to map background data (ethnicity, education level, work status) and previous medical history of general and reproductive health. The questions also included verification on pain around the vaginal opening during intercourse or tampon use, whether the pain was unprovoked or provoked, and onset of symptoms. Questions about earlier treatment and sexual function were also included.

Box 1. Procedures for Each Visit

Visit 1: Baseline—1st treatment with BTA or placebo, pain rating for intercourse or tampon use, pressure measurement, background questionnaire, FSFI, FSDS
Visit 2: 1.5 mo—pressure measurement, evaluation of adverse events
Visit 3: 3 mo—2nd treatment with BTA or placebo, pain rating for intercourse or tampon use, pressure measurement, FSFI, FSDS, evaluation of adverse events
Visit 4: 4.5 mo—pressure measurement, evaluation of adverse events
Visit 5: 6 mo—pain rating for intercourse or tampon use, pressure measurement, FSFI, FSDS, evaluation of adverse events

BTA, botulinum toxin A; FSFI, Female Sexual Function Index; FSDS, Female Sexual Distress Scale.

Pain ratings: 1) self-reported pain during intercourse or tampon insertion during the previous month using a VAS (0–100), graded in mm, was recorded at visits 1, 3, and 5; 2) a tampon test was performed weekly at home starting the week after visit 1. The participants received medium-sized tampons (circumference 43 mm, length 49 mm) to be inserted in the vaginal opening and then withdrawn. The perceived insertion pain was graded using a VAS (0–100). The mean score of the weekly tampon tests between visits was used for the statistical analyses for each visit. The results are presented as mean±SD. The results were reported in a web-based diary, where any sort of adverse event also could be reported.

The diagnosis of provoked vestibulodynia was confirmed by a cotton swab test after other causes of pain had been excluded. Assessment of the pelvic floor muscles was performed by digital palpation, with specific focus on the bulbocavernosus muscle to evaluate hyperactivity.

The pelvic floor muscle pressure was measured and recorded with a urodynamic catheter (T-DOC Air-Charged). The patients were seated in a standardized position, the 5-mm catheter balloon was inserted into the vaginal opening and carefully placed at the level of the bulbocavernosus muscles. Three parameters were recorded and evaluated in mm Hg: 1) vaginal resting pressure, 2) maximum contraction force calculated as the mean of three maximum contractions, and 3) endurance force during 10 seconds of contraction. The measurements were performed twice, and the mean values of the two measurements were used for the statistical analyses.

Validated questionnaires on sexual function were also completed. The Female Sexual Function Index is a brief self-report measure divided into six domains (desire, subjective arousal, lubrication, orgasm, satisfaction, and pain), assessing sexual function during the previous 4 weeks. Scores below the cutoff point of 26.55 indicate women with a risk of sexual dysfunction.[18,19] The Female Sexual Distress Scale is a questionnaire developed and designed to assess sexually related personal distress in women during the previous 30 days. A cutoff score of 15 or greater is considered to indicate sexual distress.[20]

The patients were randomized using a computerized block-randomization of 30 patients in three blocks. The randomization was kept in sealed envelopes and opened by a study midwife in a separate room, where she also prepared the injections. Fifty units of botulinum toxin A were diluted in saline solution to 0.5 mL. The placebo was 0.5 mL saline 9 mg/mL and prepared in an identical syringe.

During injections and pressure measurement the patients were in lithotomy position. The bulbocavernosus muscle was identified through palpation. The injections were performed with electromyography (EMG) needles (Botox injection needle [37 mm*27 G]), connected to an EMG device (Myoguide System) with pregelled surface electrodes (Kendall Nutab Diagnostic Tab Electrodes). The EMG system was used to ensure correct deposition of the drug in the muscle. Each of the two treatments consisted of four injections of 0.125 mL solution. Injection sites were in the lateral and medial portion of the bulbocavernosus muscle, part of the superficial pelvic floor muscles, and below the plane of levator ani, to achieve sufficient spread of the solution within the muscle. During the study, the participants were told to refrain from pelvic floor muscle physical therapy.

A sample size of 38 participants for each group was calculated to achieve statistical power of 80% based on an effect size of 20 units on the VAS (0–100) (mean VAS score range 56–76±31 SD).[15] Forty-four women were included in each group to provide a margin for a potential loss to follow-up. To analyze the differences in means in the outcome variables, we computed the *t* test. The posttreatment period is defined as the average of all visits after visit 1. The longitudinal structure of the data allowed us to monitor the participants across multiple follow-up visits. Using a repeated-measure design, we explored the effect of botulinum toxin A by comparing the BTA group with the placebo group across visits 1–5. For this analysis, we used ordinary least-square regressions for continuous outcomes and logistic regressions for binary outcomes. To capture the difference in differences in the outcomes across each visit, we included interaction terms between each visit and treatment status.[21] The statistical analysis was conducted using STATA 15.1.

RESULTS

One hundred twenty-four women were assessed for eligibility. Of those, 36 were excluded (32 as a result of not meeting inclusion criteria, and four declined to participate). Eighty-eight women were included and randomized, all of whom received the allocated treatment (Fig. 1). The mean duration of provoked vestibulodynia symptoms was 6 years, with no difference between the BTA and placebo groups. An overview of participant characteristics can be seen in Table 1. Most participants had tried various treatments before the study, most commonly topical lidocaine, pelvic floor physical therapy and psycho-sexual

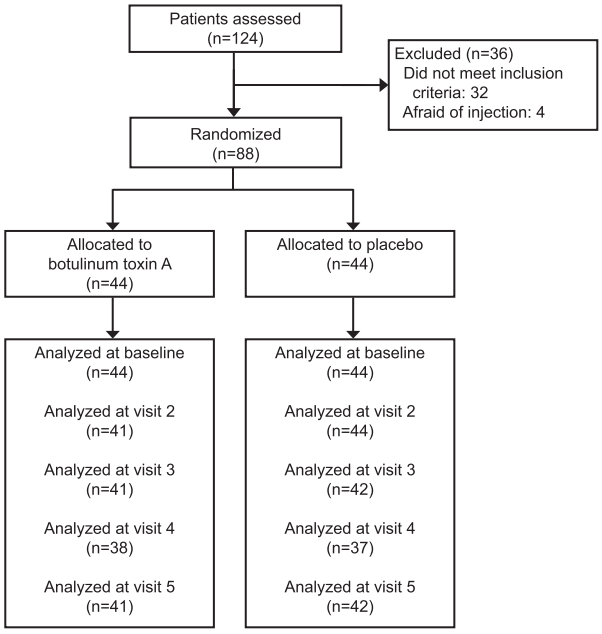

Fig. 1. Flowchart of study participants.

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counseling. Only two participants, one in each group, previously had provoked vestibulodynia surgery. Regarding mental illness, only four patients were on antidepressant drugs for mild to moderate anxiety or depression, and no change of medication occurred during the study.

No severe side effects were reported, and there were no significant differences in side effects between the groups. The most common side effect in both groups was rapidly resolving pain at the injection site. A few patients reported pain lasting a couple of days, and one patient in the placebo group reported pain for 3 weeks. One patient in the BTA group and two patients in the placebo group reported an occasional and transient problem holding urine during physical exercise.

For the primary outcome, there was no difference at inclusion in VAS score (0–100) for dyspareunia or pain at tampon use during the previous month between the BTA group (VAS mean score 68±18) and the placebo group (VAS mean score 67±25). The between-group comparison posttreatment (Fig. 2A and Table 2) showed a lower but nonsignificant pain rating on the VAS by 7 units (95% CI −15.0 to 0.4) in the BTA group compared with the placebo group. This result corresponds to an 11% decrease in pain when compared with the mean pain rating in the BTA group at baseline. The pain ratings for each group and visit are presented in Table 3. The differences in pain reduction from baseline across visits between the BTA and placebo groups (Fig. 2B) show a nonsignificant decrease in pain rating at visit 3 for the BTA group.

Figure 3A presents mean VAS score (0–100) in the weekly tampon test. Pain rating at baseline was similar between the BTA group (VAS mean score 47±23) and the placebo group (VAS mean score 54±25). Between-group comparison posttreatment showed a significant reduction of 11 VAS units in the BTA group compared with the placebo group (95% CI −16.59 to −6.03, Table 2). The lower pain rating corresponds to a 24% reduction in pain when compared with baseline mean in the BTA group. Analyzing the difference in differences in pain reduction between the BTA and placebo groups across visits, revealed no significant discrepancies (Fig. 3B).

Table 1. Characteristics of the Study Participants

Characteristic	BTA Group (n=44)	Placebo Group (n=44)
Age (y)		
Younger than 25	21 (48)	20 (45)
25–29	18 (41)	18 (41)
30–34	2 (5)	6 (14)
Older than 34	3 (7)	0 (0)
Socioeconomic status		
Study	12 (27)	8 (18)
Work	25 (57)	27 (61)
Work and study	5 (11)	9 (20)
Unemployed	2 (5)	0 (0)
Permanent partner	35 (80)	34 (77)
Immigrant	6 (14)	2 (5)
Other conditions		
Migraine	5 (11)	5 (11)
IBS	15 (34)	6 (14)
Back pain	20 (45)	23 (52)
Muscular pain	4 (9)	8 (18)
Mental disorder	8 (18)	10 (23)
Menstrual pain	31 (70)	30 (68)
Painful urination	6 (14)	7 (16)
History of infections		
Yeast infection	36 (82)	33 (75)
Herpes	2 (5)	5 (11)
UTI	29 (66)	27 (61)
Bacterial vaginosis	11 (25)	4 (9)
Type of provoked vestibulodynia*		
Primary	22 (50)	16 (36)
Secondary	24 (56)	27 (63)

BTA, botulinum toxin A; IBS, irritable bowel syndrome; UTI, urinary tract infection.

Data are n (%).

* Primary provoked vestibulodynia, pain at first tampon insertion or intercourse attempt; secondary provoked vestibulodynia, pain at tampon use or vaginal intercourse, with a prior history of a pain-free period.

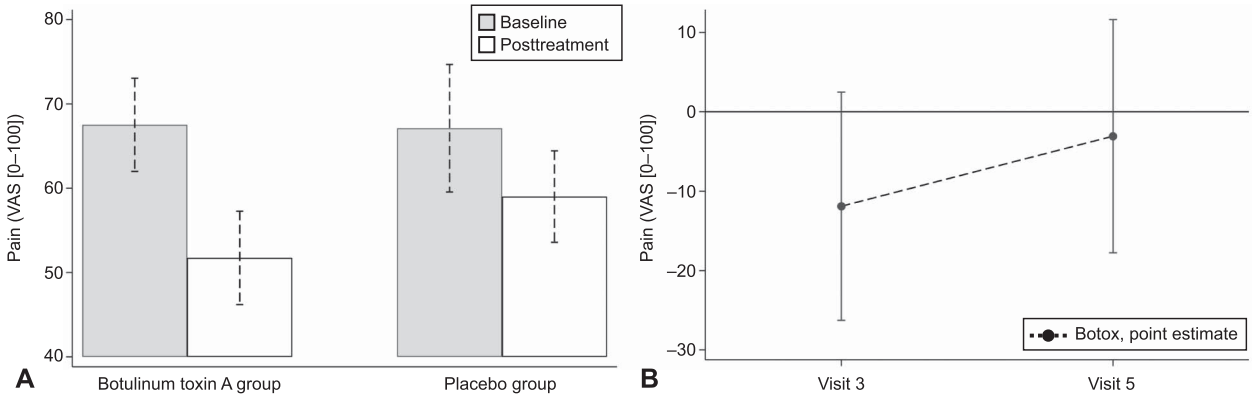

Fig. 2. Self-reported dyspareunia or pain at tampon use during the previous month. **A**. The means and CIs in pain rating (visual analog scale [VAS] score [0–100]) for the BTA (botulinum toxin A) and placebo groups separately at baseline (visit 1) and posttreatment (visits 3 and 5). **B**. Difference-in-differences in pain rating (VAS scores [0–100]) across visits 3 and 5. The results are presented as regression coefficients and 95% CIs.

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The BTA group had a significant lower vaginal resting pressure at baseline (mean 20 mm Hg±7) than the placebo group (mean 24 mm Hg±10, Table 2). No significant effect was found when comparing differences across visits.

The maximum contraction strength at baseline was not significantly different between the BTA group (mean 34±21 mm Hg) and the placebo group (mean 32±20 mm Hg). Between-group comparison posttreatment (visits 2–5) showed a significant reduction of 7 mm Hg in the BTA group compared with the placebo group (95% CI −12.70 to −2.38, Figure 4A and Table 2). When analyzing the differences in maximum contraction force across visits, no significant effect of botulinum toxin A was found (Fig. 4B).

Table 2. Primary and Secondary Outcomes in the BTA (Botulinum Toxin A) and Placebo Groups at Baseline and Posttreatment

	Baseline		Posttreatment*				
					t test		
Outcome	BTA Group	Placebo Group	BTA Group	Placebo Group	*t* statistic	Difference	95% CI
VAS score (0–100)							
Dyspareunia or pain at tampon use	67.5±18.2	67.1±24.9	51.7±25.7	59.0±25.0	−1.86	−7.27	−14.97 to 0.44
Pain at tampon use	46.7±23.4	54.0±25.0	39.2±23.2	50.5±25.7	−4.21	−11.31†	−16.59 to −6.03
Vaginal resting pressure (mm Hg)‡	19.6±6.6	24.5±10.1	17.4±5.6	23.0±8.9	−5.82	−5.59†	−7.48 to −3.70
Maximum contraction strength (mm Hg)	33.8±21.1	32.1±20.2	26.7±24.2	34.2±22.0	−2.88	−7.49§	−12.70 to −2.38
Pelvic floor muscle endurance (mm Hg)	20.4±15.2	20.5±15.6	16.6±14.1	21.0±15.6	−2.66	−4.44§	−7.72 to −1.16
FSDS score	33.4±10.6	29.9±9.2	29.3±12.6	26.7±10.4	1.42	2.56	−0.99 to 6.11
FSFI score	20.4±4.0	17.9±3.4	20.9±6.8	19.5±5.9	1.19	1.37	−0.90 to 3.67
Intercourse (proportion)	0.432±0.501	0.341±0.479	0.73±0.45	0.46±0.50	2.54	0.27‖	0.06–0.48

BTA, botulinum toxin A; VAS, visual analog scale; FSDS, Female Sexual Distress Scale; FSFI, Female Sexual Function Index.
Data are mean±SD unless otherwise specified.
* Differences in means between the BTA and placebo groups in the posttreatment period are computed using two-sample *t* test.
† $P<.001$.
‡ Vaginal resting pressure is statistically different between the BTA and placebo groups at baseline. All other outcome variables are statistically nonsignificant at baseline.
§ $P<.01$.
‖ $P<.05$.

Table 3. Visual Analog Scale Scores at Each Visit for the Primary Outcome of Dyspareunia or Pain at Tampon Use During the Previous Month

Visit	BTA Group	Placebo Group	*t* test*		
			t statistic	Difference	95% CI
Visit 1	67.5±18.2	67.1±24.9	0.09	0.41	−8.82 to 9.64
Visit 2	50.3±25.1	61.8±23.6	−2.21	−11.49†	−21.82 to −1.16
Visit 3	53.3±26.5	55.9±26.4	−0.45	−2.66	−14.37 to 9.05

Data are mean±SD unless otherwise specified.
* Differences in means between the BTA and placebo groups in the posttreatment period are computed using two-sample *t* test.
† $P<.05$.

The ability to keep the contraction for 10 seconds was analyzed. At baseline, there was no difference in pelvic floor muscle endurance between the BTA group (mean 20±15 mm Hg/10 s) and the placebo group (mean 20±16 mm Hg/10 s). Between-group comparison suggests that botulinum toxin A injections were associated with a significant decrease in endurance by 4 mm Hg/10 s (95% CI −7.72 to −1.16, Figure 5A). This corresponds to a decrease in endurance by 22% when compared with the mean endurance in the BTA group at baseline. Analyzing the differences across visits between botulinum toxin A and placebo, no significant discrepancies were found (Fig. 5B).

For all participants attempting intercourse (n=34 at baseline), the Female Sexual Function Index score at baseline for the BTA group (mean 20±4) and the placebo group (mean 18±3) suggests sexual dysfunction in both groups. Posttreatment, there was no significant change in the scores between the groups (Table 2).

At baseline, there was no significant difference in Female Sexual Distress Scale scores between the BTA group (mean 33±11) and the placebo group (mean 30±9). Posttreatment, there was no significant change in the scores between the groups (Table 2). The pretreatment and posttreatment scores were all within the range of sexual distress (ie, 15 or greater).

At baseline, there was no significant difference in intercourse activity between the BTA and placebo groups. In the BTA group, 43% were engaged in intercourse activity at baseline, as compared with 34% in the placebo group. Between-group comparison at visit 5, showed a significant increase in intercourse activity in the BTA group by 27% compared with the placebo group (Table 2). When comparing the differences between the groups, no significant effect was found.

DISCUSSION

The aim of this study was to evaluate pain reduction after two treatments of 50 units of botulinum toxin A in women with provoked vestibulodynia. The result of the primary outcome showed no clinically meaningful reduction of dyspareunia or pain at tampon use for

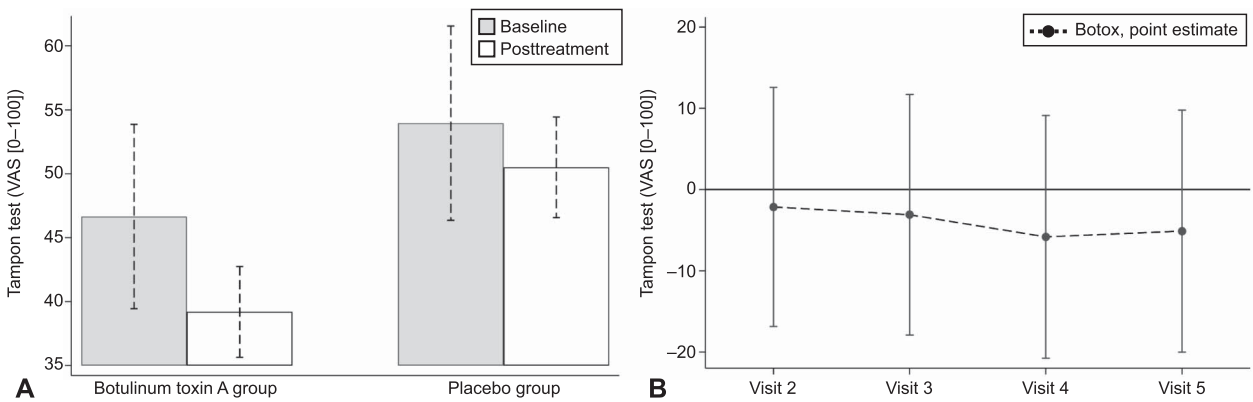

Fig. 3. Tampon test. **A**. The means and CIs in pain rating (visual analog scale [VAS] score [0–100]) for the BTA (botulinum toxin A) and placebo groups separately at baseline (visit 1) and after treatment (visits 2–5). **B**. Difference-in-differences in pain rating (VAS scores [0–100]) across visits 2–5. The results are presented as regression coefficients and 95% CIs.
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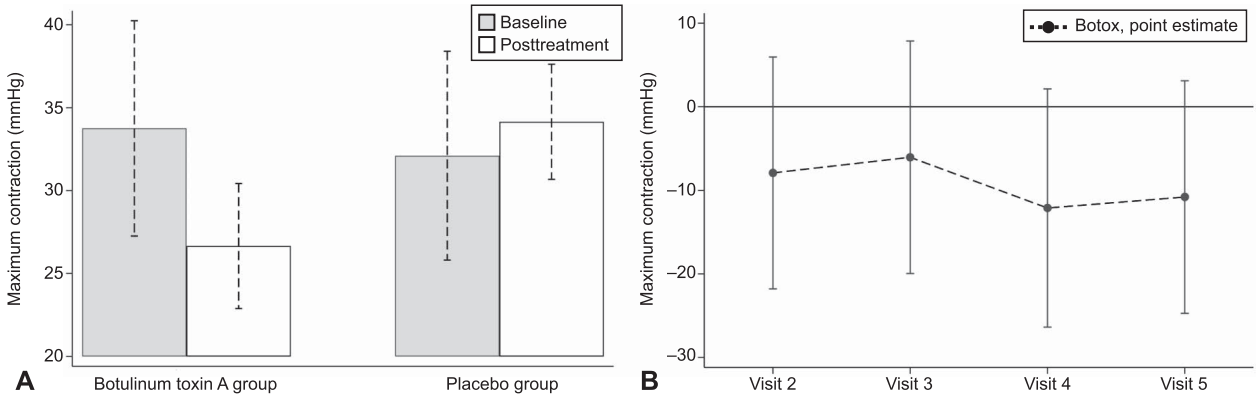

Fig. 4. Maximum contraction force (mm Hg). **A**. The means and CIs in maximum contraction force (mm Hg) for the BTA (botulinum toxin A) and placebo groups separately at baseline (visit 1) and posttreatment (visits 2–5). **B**. Difference-in-differences in maximum contraction force (mm Hg) across visits 2–5. The results are presented as regression coefficients and 95% CIs.

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the BTA group compared with the placebo group. However, considering the results of the secondary outcomes, botulinum toxin A appears to reduce pain at tampon use, reduce pelvic hypertonicity and increase sexual activity to some extent.

Petersen et al,[15] found a significant pain reduction after 20 units botulinum toxin A in both the BTA and placebo groups after a single treatment, with no difference between the groups. Based on the result of that study, we increased both dosage and number of treatments to achieve a possible further pain reduction. Lately, more data on off-label use of botulinum toxin A for provoked vestibulodynia have been reported using even higher doses. In a recent, small randomized controlled trial, no effect was shown after a subcutaneous single injection of either 50 or 100 units of botulinum toxin A; however, when still-symptomatic patients were offered an additional 100-unit injection after 3 months, this resulted in a significant reduction in VAS scores, which further emphasizes that the effect of botulinum toxin A is most likely related to dosage and number of treatments.[22]

We used the tampon test in an effort to standardize outcome measures and to provide a feasible way to analyze all patients, regardless of sexual activity.[23,24] The weekly tampon test effectively demonstrates the onset and duration of the botulinum toxin A effect. A decrease in VAS score was seen approximately 5 weeks after both injections, which is in line with previous studies showing an expected maximum effect after a few weeks and duration of up to 3–4 months.[25,26]

The dose and injection technique used exhibited few side effects. The overall reported adverse events

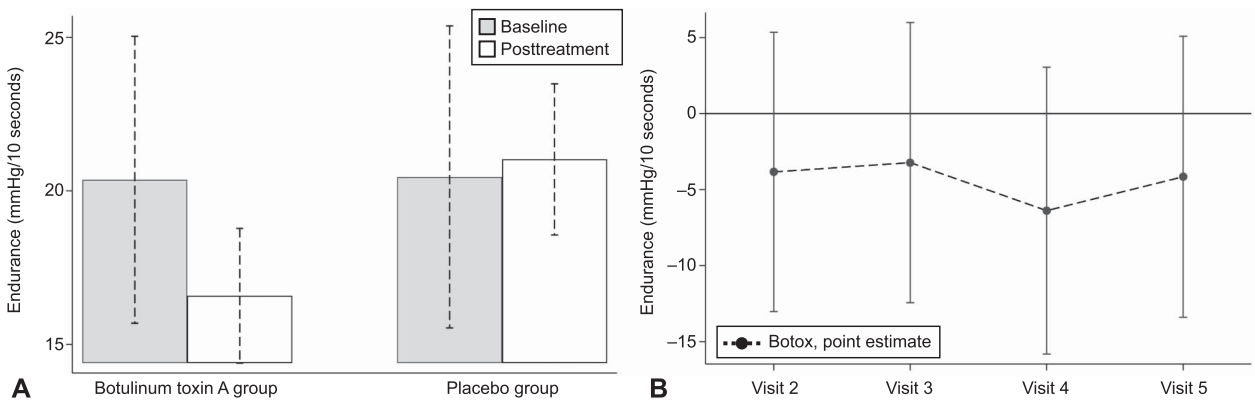

Fig. 5. Endurance (mm Hg/10 s). **A**. The means and CIs in endurance (mm Hg/10 s), for the BTA (botulinum toxin A) and placebo groups separately at baseline (visit 1) and posttreatment (visits 2–5). **B**. Difference-in-differences in endurance (mm Hg/10 s) across visits 2–5. The results are presented as regression coefficients and 95% CIs.

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were few and transient, and no severe adverse events were reported. One side effect was mild, transient urine leakage during physical exercise, which has not been reported before.[15,22] This occurred in both groups.

The aim of using botulinum toxin A in previous studies has mainly been pain reduction solely, and discussion of pelvic floor hypertonicity is scarce.[15,22] In our study, pelvic floor muscle hypertonicity was defined by digital palpation, and one of our hypotheses was that improvement of dyspareunia would be secondary to muscle relaxation. The vaginal manometer was used in an attempt to objectively measure possible treatment effects on the muscular response, and we could see a reduction in muscle strength and endurance in the BTA group. However, we chose to inject the bulbocavernosus muscles, which are easy to access and inject intravaginally. The medial injection site is close to the superficial part of the levator ani, and a diffusion of the toxin to this muscle might have occurred.[27,28] Additional treatment effect might be achieved if other parts of the pelvic floor muscles are injected as well.[29] In this study, the participants were told to refrain from pelvic floor muscle physical therapy to avoid bias. However, in clinical practice, a botulinum toxin A treatment in combination with physical therapy will most likely have an additive effect on the muscle response.

A positive effect of the botulinum toxin A injections was a significant increase in number of women engaging in vaginal intercourse posttreatment. This was despite no improvement in overall sexual function and distress as measured by the Female Sexual Function Index and the Female Sexual Distress Scale. One reason for this contradictory finding could be that the moderate pain reduction seen was too low to improve sexual function or that the follow-up period of 6 months was too short to detect any change.

The major strength of this study is the design, being a double-blinded randomized trial. Both groups were similar at baseline for most outcome variables and few patients were lost to follow-up. A limitation, however, is, as with most studies on provoked vestibulodynia treatment, the lack of consensus on outcome measures.[30] In this study, the primary outcome was self-reported pain at vaginal intercourse or pain at tampon use the recent month, but the results revealed that many of the participants were not having intercourse nor using a tampon regularly. This limitation was partly circumvented by using the tampon test as a secondary outcome measure. Another limitation is lack of validation of the vaginal pressure measurement method before the study. The results suggest improvements in most secondary outcome variables in the BTA group, superior to the placebo group, with a magnitude of approximately 10–25%. However, these results are not consistently significant. With a larger sample size, it is possible that these differences would reach statistical significance.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Not available.*

What other documents will be available? *Not available.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable.*

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