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Botulinum toxin-treatment of localized provoked vulvodynia refractory to conventional treatment

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ABSTRACT

Introduction: We wanted to evaluate the efficacy of botulinum toxin type A (botulinum toxin) treatment on vulvodynia refractory to conventional treatment.
Material and methods: A follow-up study on botulinum toxin treatment was conducted at Aarhus University Hospital (n = 109). Seventy-nine completed the follow-up. The women included had localized provoked vulvodynia, refractory to first line treatment and were treated with 100*I.E. botulinum toxin electromyography (EMG) guided in the musculus levator ani in the period from March 2012 to May 2015 (1). The outcome measures were: Dyspareunia, Negative Interference in Quality of Life (NIQL) and cotton swab test all rated on the numerical rating scale (NRS) and active vitae sexualis. Follow-up was conducted at six months.
Results: The women experienced significant improvements on, dyspareunia, which decreased to 5.82 from 7.82 ($p < 0.01$), NIQL to 6.19 from 7.88 ($p < 0.01$) and the cotton swab test to 5.50 from 6.81 ($p < 0.01$). No significant effect on Active Vitae Sexualis was found ($p = 0.25$).
Conclusion: Women injected with 100*I.E. botulinum toxin EMG guided, diagnosed with localized provoked vulvodynia refractory to conventional non invasive treatment, had a reduction in dyspareunia and improved quality of life. Injection of botulinum toxin had no significant effect on vitae sexualis. Randomized controlled trials are, however, much needed.

Introduction

Vulvodynia is defined as chronic vulvar discomfort, most commonly described as a burning, stinging pain associated to allodynia and hyperalgesia [1]. Vulvodynia is characterized by vulvar pain of at least 3 months' duration, without a clear identifiable cause, which may have potential associated factors [1,2].

Treatments can be divided and sorted by invasiveness. The first therapeutic step (non-invasive) is physiotherapy, cognitive behavioural therapy and supportive psychotherapy. Botulinum toxin can be used as the second therapeutic step (minimally invasive). The third step (invasive), when used, is surgical [1,3]. Examples of pain syndromes, which have been successfully treated with botulinum toxin treatment, are interstitial cystitis and migraine [4–6]. It is well known that botulinum toxin acts by blocking the release of acetylcholine from the presynaptic terminal of the neuromuscular junction, Thereby leading to a chemodenervation and a temporary muscle paralysis [7]. Botulinum toxin is effectively used as treatment of multiple pain syndromes. There are a lot of theories on how botulinum toxin can alter pain perception. It could be through direct effects on muscle nociceptors, influence on sensitizing mediators, physiological changes in reflex and synergistic movements, direct and secondary autonomic effects, and induced neuroplasticity in the CNS [8].

Vulvodynia, vaginismus, and chronic pelvic pain are diagnoses where botulinum toxin treatment in recent years has been introduced. These syndromes are all dominated by genital pain that interfere with the patient's sexual life [9].

In 2004 the first clinical study was published [10]. It included 12 women with chronic pelvic pain, which showed significant improvement after botulinum treatment.

Bertolasi et al. [12] performed an open-label study with 39 patients with vulvar vestibular syndrome and vaginismus. The treatment was repeated in cycles, with an average dose of 20 units per session. The repeated cycles led to sustained improvement throughout treatment cycles [12].

Abbreviations: EMG, electromyography; NIQL, negative interference in quality of life; NRS, numerical rating scale; Botulinum toxin, botulinum toxin type A.

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Two randomized controlled trials have also been conducted on chronic pelvic pain. Abbott et al. [13] conducted the first study, which included 60 women with chronic pelvic pain for at least two years, whom were treated with 80 units of botulinum toxin in m. pubococcygeus and m. puborectalis. No consideration to former treatment was taken. The botulinum toxin-group showed improvements on both visual analog scale for pain (VAS) and dyspareunia, but not statistically significant when compared to placebo [13].

The other randomized study is the only study concerning vulvodynia (Petersen et al. [4]). Twenty units of botulinum toxin were injected EMG-guided into m. bulbospongiosus in sixty-four women. Women treated with botulinum toxin before inclusion were excluded, but otherwise there was given no comment on prior treatment [4]. There was no statistically significant difference in cotton swab test VAS, 36-item Short-Form Health Survey (quality of life) or Female Sexual Function Index (FSFI), when compared to placebo.

The aim of the present study was to evaluate the botulinum toxin treatment at Aarhus University Hospital as last line of treatment of localized provoked vulvodynia.

Material and methods

Study design

Participants in the study were women referred with localized provoked vulvodynia to the vulva clinic at Aarhus University Hospital a tertiary centre of vulvodynia. First, they underwent non-invasive treatment for six to 12 months. It consisted of classes in desensibilization, physiotherapy administered by special trained physiotherapists, contraceptive pill pause and if postmenopausal vaginal oestrogen treatment. This proved inadequate for 109 women who still reported a cotton swab NRS of at least five and were therefore enrolled in the study. The women completed two questionnaires, one at baseline before the botulinum toxin injections and one at six months follow-up. At enrollment the patients underwent gynecological evaluation to exclude any ongoing vulvar pathology and a cotton swab test was performed. The cotton swab test was performed with one light touch at all four meatuses of the paraurethral- and bartholin glands. The women were followed up at six months (five to eight months) with a cotton swab test and a consultation.

Inclusion and exclusion criteria

The study inclusion criteria were: i) Vulvodynia for at least six months, ii) a NRS-score of at least five by the cotton swab test and iii) undergone desensitization and physiotherapy iv) first time treatment with botulinum toxin in the vulva in the period March 2012 – May 2015 at Aarhus University Hospital.

The study exclusion criteria were i) previous treatment with botulinum toxin in the genitalia, ii) on-going infection in the vulva or pelvis, iii) pregnancy, iv) present pathology of the vulva, v) an atypical neurological examination, vi) severely lowered respiratory capacity and vii) neuromuscular disease.

Treatment

The treatment was performed at Aarhus University Hospital, where the patient was placed in supine position in stir ups and all treated by the same consultant gynaecologist. Before injection, a local analgesic (25 mg lidocaine and 25 mg prilocaine per g creme) was smeared at the injection sites. 100 units of botulinum toxin was used per patient, diluted into 1 ml isotonic saline. It was evenly distributed bilaterally (50 units each site) and injected into m. levator ani pars pubo rectalis under EMG guidance using the Desitin Xeomin® EMG kit. The target of injection was five to 10 mm below the vaginal epithelium approximately one cm on the vaginal side of the hyminal ring at four and eight o'clock. The patient was informed that the treatment should be supported by continued self-stretching, desensitization and dilatation program as prior to treatment.

The Danish Data Protection Agency approved the study protocol (Region Midtjylland jr. nr 1-16-02-645-15). The women filled out a written consent.

Outcome measures

Dyspareunia

Pain associated with sexual intercourse, last time tried, defined on the NRS from 0 to 10, where "0″ was described as" no pain at all" and "10″ was described as "the worst pain you could ever imagine".

Negative interference in quality of life (NIQL)

To which degree vulvodynia interferes with everyday life on the NRS from 0 to 10, where "0″ was described as "no interference with the quality of my every day life" and "10″ was "it interferes with every moment of my every day life in a negative manner".

Cotton swab test

Reported by the women, when cotton swab tested, on the NRS from 0 to 10, where "0″ was defined as" no pain at all" and "10″ as" the worst pain you could ever imagine".

Active vita sexualis

The women were asked whether or not they had an active vitae sexualis. This does not necessarily mean coitus, but engaging in sexual activities.

Statistical analyses

The outcome measures were compared by average values before botulinum toxin treatment and at the 6 months follow-up. The changes in dyspareunia, NIQL and cotton swab NRS before and after treatment were significance tested with a dependent T-test, with significance level at $p < 0.05$.

Results

Baseline characteristics

109 women were included, 30 had dropped out by follow-up. The remaining 79 patients were followed up. The patients were divided in groups by age of under and over 30 years of age, to screen for age related differences. There were no notable differences between the group under and the group over 30 years of age (Table 1).

Outcomes

Dyspareunia NRS decreased to 5.82 from 7.82, $p < 0.001$ and NIQL NRS decreased to 6.19 from 7.88, $p < 0.001$ (Table 2 and Fig. 1). The changes in dyspareunia and NIQL are illustrated in box plot, Fig. 1.

The patients reported a statistically significant reduction in cotton swab test mean NRS to 5.50 at follow-up compared to 6.81 at baseline, $p < 0.001$ (Table 2). The changes in cotton swab NRS are illustrated in box plot, Fig. 1.

Active vita sexualis showed a tendency towards improvement but without being statistically significant ($p = 0.25$).

In our cohort one patient had a history of endometriosis diagnosed by laparoscopy. This patient was treated with

Table 1
Baseline characteristics of patients.

	Age < 30	Age ≥ 30	All
Number (%)	48 (60)	31 (40)	79 (100)
Age mean (SD)	–	–	31.78 (12.77)
Paraurethral gl. left mean (SD)	6.45 (2.36)	6.35 (2.21)	6.42 (2.29)
Paraurehtral gl. right mean (SD)	6.19 (2.47)	5.96 (2.54)	6.11 (2.48)
Bartholin gl. left mean (SD)	7.67 (1.97)	7.30 (1.56)	7.55 (1.84)
Bartholin gl. right mean (SD)	7.29 (2.12)	7.00 (2.20)	7.19 (2.13)
Active sexual life yes n (%)	23 (48)	12 (39)	35 (44)
Active sexual life no n (%)	10 (21)	7 (23)	17 (22)
Active sexual life Missing n (%)	15 (31)	12 (39)	27 (34)
Dyspareunia (SD)	7.93 (2.02)	7.77 (2.83)	7.88 (2.27)
NIQL - Negative interference of quality of life (SD)	8.07 (1.60)	7.67 (2.06)	7.95 (1.73)

Paraurethral gland left mean = Numerical rating scale of pain from 0 to 10 when cotton swab tested; Paraurethral gland right mean = Numerical rating scale of pain from 0 to 10 when cotton swab tested; Bartholin gland left mean = Numerical rating scale of pain from 0 to 10 when cotton swab tested; Bartholin gland right mean = Numerical rating scale of pain from 0 to 10 when cotton swab tested; Dyspareunia = Pain rating as associated with sexual intercourse defined on a numerical rating scale from 0 to 10; NIQL = To which degree vulvodynia interferes with everyday life on a numerical rating scale.from 0 to 10.

Table 2
Baseline compared to follow-up at 6 months after botulinum toxin treatment. The patients are compared by the cotton swab test, dyspareunia and NIQL (negative interference of quality of life). Dyspareunia, NIQL and NRS are rated with NRS-score = numerical rating scale score on a scale from 0 to 10.

	(*n*)	Baseline	6 month follow-up	Difference	P-value
Cotton swab test	63	6.81	5.50	1.31	< 0.01
Dyspareunia	44	7.82	5.82	2.00	< 0.01
NIQL	42	7.88	6.19	1.69	< 0.01

GNRH-agonist and later Gestagen IUD with good effect on the deep dyspareunia.

Three patients had a history of lower bag pain. One patient where conservatively treated for lumbal disc protrusion. The two other patients had prior to the study had surgery in the back, one patient due to scoliosis and one due to disc protrusion. No sign of nerve compression were noted.

Five patients reported urine incontinence as a side effect in the first days/weeks after treatment. In none of the cases did urine incontinence persist at the six months follow up. No other side effects have been reported.

Discussion

This study shows that patients with provoked localized vulvodynia refractory to conventional treatment treated with EMG-guided botulinum toxin experienced an improved quality of life and decrease in pain during intercourse (Table 2 and Fig. 1). The patients had all gone through six to 12 months of desensibilization, physiotherapy, contraceptive pill pause and if postmenopausal vaginal oestrogen treatment with no satisfactory result.

In this study, the patients were highly selected. All the patients had a long history of vulvodynia. They had shown refractory to 3–4 kinds of treatment before inclusion and vulvodynia was still a

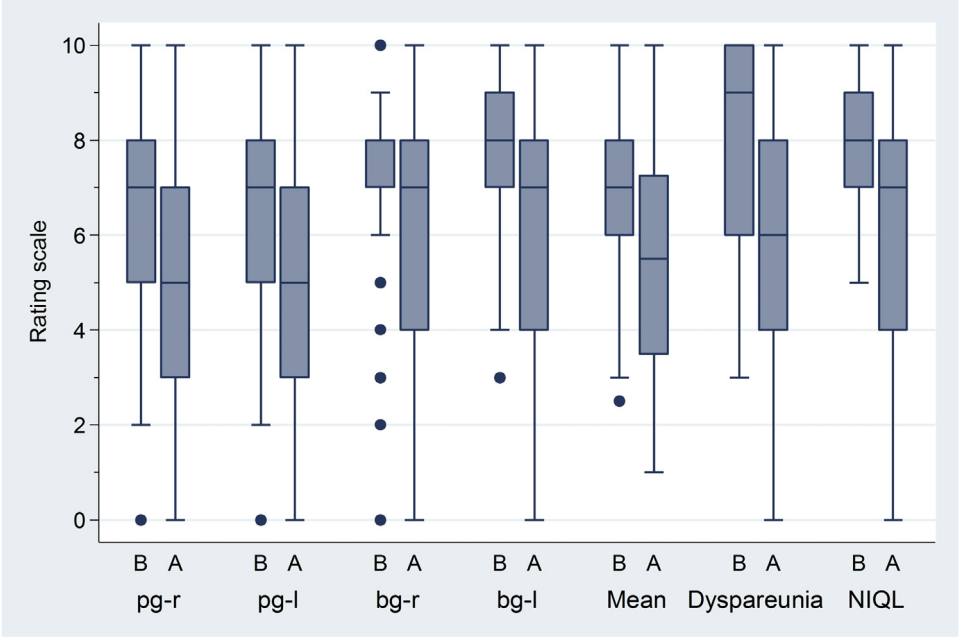

Fig. 1. Box plot showing baseline and 6 months follow-up on outcome measures after botulinum treatment of vulvodynia (n = 79). The boxes represent the data between the 25 percentile to the 75 percentil, the line in the middle of the boxes the median.
B = Before; A = After; NRS at the parauretral gland (right = pg-r; left = pg-l); NRS at the bartholin gland (right = bg-r; left = bg-l); Mean = The average NRS of both bartholine glands and both paraurethral glands; Dyspareunia = Dyspareunia; NIQL = Negative Interference in Quality of Life.

considerable burden in the women's everyday life. Furthermore, the positive cotton swab test was included as an objective inclusion criteria at NRS > 5. All of the above-mentioned criteria's for diagnosis and inclusion, makes the study specific and reproducible.

The continued self-stretching, desensitization and dilatation after botulinum toxin treatment, could contribute to an overestimation of the effect of botulinum toxin treatment. However, before inclusion the women had already gone through the self-stretching, desensitization and physiotherapy for months without a satisfactory result. The lack of a placebo group weakens the study's external validity and thereby comparability to other studies. The scales used in this study to quantify sexual function and quality of life has not been validated and the parameters would be more quantifiable if a validated questionnaire had been used to objectify sexual function and quality of life, e.g. female sexual function index (FSFI), Female Sexual Distress scale (FSDS) or 36-item Short-Form Health Survey (SF-36) [4,14].

As opposed to the two randomized controlled studies, this study is focusing on women that have tried 3–4 different treatments with an unsatisfactory result [4,13]. Severe side effects have been second to none in all studies. Petersen et al. is the only randomized study on women diagnosed with vulvodynia. The amount of botulinum toxin was only 20 units compared to our 100 units and was more superficially injected in m. bulbospongiosus.

No consensus has been reached as to how and at what location botulinum toxin should be administered. There has been a substantial difference in the amount of botulinum toxin used in other studies (20–100 units). In most studies botulinum toxin has been administered as a single dosage. Three studies have indicated better outcomes when botulinum toxin was given in higher doses and/or cyclical [11,12,15].

The research until now has only to a lesser extend addressed the considerations of how botulinum toxin should be injected to achieve the highest effect (EMG, multiple injection sites, sub cutaneous injection, with or without prior local anaesthesia) [11,12]. Our study indicates EMG-guided botulinum toxin injections into musculus puborectalis, given as a single dosage has a positive effect on provoked vulvodynia.

Conclusion

Our study shows that botulinum toxin used as last line of intervention for refractory vulvodynia may be a useful tool. Patients, with localized provoked vulvodynia refractory to conventional treatment, showed significant decrease in dyspareunia and Negative Interferrence in Quality of Life when treated with botulinum toxin. However, a large randomized placebo-controlled study is much needed regarding injection site, dose and repetitive treatment.

Conflict of interest statement

There are no potential conflicts of interests and financial disclosures in connection with this article.

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