ORIGINAL RESEARCH—PAIN

Botulinum Toxin Type A—A Novel Treatment for Provoked Vestibulodynia? Results from a Randomized, Placebo Controlled, Double Blinded Study

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ABSTRACT

Introduction. Vestibulodynia is an increasingly recognized problem among women and is often difficult to treat.
Aim. This randomized, double blinded, placebo-controlled study aimed to evaluate the efficacy of Botox in the treatment of vestibulodynia.
Methods. Sixty-four women were randomized to receive Botox (N = 32) or saline placebo (N = 32). Botulinum toxin A (20 I.E.) diluted in 0.5 mL saline or 0.5 mL saline was injected in the musculus bulbospongiosus at baseline.
Main Outcome Measures. Pain was measured monthly on a visual analog scale (VAS) Likert scale. Sexual function was measured using the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale at baseline and at 3 and 6 months follow up. Quality of life was measured using the 36-item short-form (SF-36).
Results. Sixty women (94%) completed the 6 months follow up. Both Botox and placebo produced significantly pain reduction ($P < 0.001$). There was no significant difference in the median VAS score between the groups at 6 months follow up ($P = 0.984$). An improvement on the FSFI full score from baseline until 6 months was not significantly different between the groups ($P = 0.635$).

In the placebo group a statistical significant larger reduction in sexual distress was observed from baseline until 6 months follow up compared to the Botox group ($P = 0.044$). No statistical significant differences were observed between the B- and P-groups in regard to the SF-36 scores.
Conclusion. Injection of 20 I.E. Botox in the vestibule of women diagnosed with vestibulodynia does not reduce pain, improve sexual functioning, or impact the quality of life compared to placebo and evaluated at 3 and 6 moths follow up. Both the Botox group and the placebo groups experienced a reduction in pain on the VAS Likert scale at 6 months follow up. Women with vestibulodynia have difficulty with sexual function and present with sexual distress, which has to be addressed in conjunction with pain to eliminate the disorder. **Petersen CD, Giraldi A, Lundvall L, and Kristensen E. Botulinum toxin Type A—A novel treatment for provoked vestibulodynia? Results from a randomized, placebo controlled, double blinded study. J Sex Med 2009;6:2523–2537.**

Key Words. Botulinum Toxin; Vestibulodynia; Provoked Vestibulodynia; Vulvar Pain Syndrome; Pelvic Pain; Dyspareunia; Quality of Life; Sexual Dysfunction; Sexual Pain; Vulvar Disease

Introduction

Vulvar pain occurring in the absence of visible clinical findings is an increasingly recognizable problem among women, often leading to chronic dyspareunia, chronic pelvic pain (CPP), and other sexual health problems [1]. Vulvar pain is reported to have a prevalence rate of 15% among women in the general population [2]. Vulvodynia, defined by the International Society for the Study of Vulvar Diseases as chronic discomfort in the vulva, is often described as a burning pain

without objective findings or specific signs of a neurological disorder [3]. Vulvodynia is classified according to: (i) the localization of the pain in the vulva, (ii) whether it is generalized or localized, and (iii) whether it arises on provocation of the area or occurs spontaneously. The pain may also be found in a mixed form, whereby it is found both on provocation and spontaneously. The localized, provoked form of vulvodynia at present time named vestibulodynia is diagnosed based on the Friedrisch triad which includes the following three diagnostic criteria: (i) pain when attempting to insert an object into the vagina, (ii) pain on pressure to the vestibule, and (iii) vestibular erythema.

It has been shown that women suffering from provoked vestibulodynia often complain of long term sexual inactivity, are known to be mildly to moderately depressed, and experience high levels of anxiety as well as poor quality of life [4,5].

The etiology of localized, provoked vulvodynia has been extensively investigated and many factors have been proposed, including infectious, inflammatory, embryological, genetic, hormonal, and mechanical etiologies [6,7]. Many of these factors may induce pathophysiological changes in three interdependent systems: (i) nervous system pain regulatory pathways, (ii) pelvic floor muscles, and the patient's psychosocial, and (iii) sexual function [8].

Studies have demonstrated local intraepithelial neural hyperplasia of C-fibers in the vestibular tissue, signs of peripheral nociceptor sensitization, and findings of various pain neurotransmitters such as glutamate and substance P, which may lead to chronic neuropathic pain [9,10]. Hyper tonicity of the pelvic floor muscles is another potential contributing factor to this chronic pain condition [11].

Recently vulvodynia has been described as a variant of limbic associated pelvic pain (LAPP), which is hypothesized to occur in patients with CPP without any demonstrable pathology (hyperalgesia) and with more than one demonstrable pain generator (allodynia). LAPP may be caused by alterations in the pain processing pathways in the central nervous system or dysfunction in the limbic system, which can be demonstrated by cortical changes found in fearful pain [12]. The eliciting factors or stressors have not yet been isolated, but a history of abuse or trauma is predominant in CPP patients. Limbic dysfunction is demonstrated by a cycle of increased sensitivity to pain afferents from pelvic organs, and abnormalities in the efferent innervations of the pelvic musculature (including visceral as well as somatic) pain afferents in the medial pain pathways back to the sensitized organs, along with a hyper vigilant limbic system and efferent stimulation of the pelvic muscles leading to hyper tonicity. Disruption of this cycle often produces relief. However, without full disruption of the peripheral and central dysfunction of the nervous system and the limbic hypervigilance, pain may recur. Thus there is a continued need to develop and evaluate potential treatment options to control this pain cycle [12].

Multiple treatments, including topical lidocaine, antidepressants, cognitive behavioural therapy, vestibulectomy, and electromyographic (EMG) biofeedback have been studied [13]. An increasing number of these treatments have been evaluated in randomized studies with promising results, reporting decreasing dyspareunia and improved quality of life with treatment. However, most trials have not reported full recovery with these interventions [14–16].

Recently, Botulinum toxin (Botox®) has been introduced as a potentially beneficial agent for the treatment of vestibulodynia. Botulinum toxin A (BTX-A) is a neurotoxin, successfully used in the treatment of vaginismus and other medical conditions such as migraine, palmar hyperhidrosis, torticollis, cerebral palsy, interstitial cystitis, blepharospasm, and myofacial pain. BTX-A inhibits the release of the acetylcholine neurotransmitter from the pre-synaptic region of the neuromuscular junction, thus leading to chemodenervation and a temporary muscle paralysis [17,18]. Recent studies have suggested that Botox also acts as a novel analgesic in therapy resistant chronic pain syndromes such as myofacial pain syndromes, migraines, and chronic tension-type headache [18]. In vivo animal research suggests that the neurotoxin has an anti-nociceptive effect that is independent of its neuromuscular activity, which works by inhibiting the release of neurotransmitters such as glutamate, substance P, calcitonin gene-related peptide, and histamine. This blockage inhibits peripheral sensitization of nociceptive fibers and indirectly reduces central sensitization [19]. Studies of women with vaginismus also speculated that Botox blocks the nociceptive receptors in the submucosal layers of the vestibule and decreases hypertonicity of the pelvic floor through muscle paralysis [20]. The effect of Botox is known to last a minimum of 3 months and generally up to 6 months. Since 2004, an increasing number of pilot studies on the effect of injections of Botox intramuscularly or into the vestibule on women suffering from vestibulodynia have