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Sexual Dysfunction

A Retrospective Study of the Management of Vulvodynia

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Purpose: Vulvodynia is characterized by chronic vulvar pain caused by sexual intercourse and often results in female sexual dysfunction. Because the causes of vulvodynia are not clear, many patients do not receive optimal treatment. Recently, gabapentin and botulinum toxin A have both been shown to be effective treatments for vulvodynia. In this study, we retrospectively analyzed the clinical outcomes of botulinum toxin A and gabapentin treatment for chronic pain in women with this condition.

Materials and Methods: Seventy-three women with vulvar pain were administered either gabapentin (n=62) or botulinum toxin A (n=11) injections. Effectiveness was measured by use of a visual analogue scale (VAS). We analyzed the treatment method, treatment duration, success of treatment, and side effects or adverse reactions.

Results: Pain levels in both groups significantly decreased after treatment. In the gabapentin group, the VAS score decreased from 8.6 before treatment to 3.2 after treatment ($p < 0.001$). The VAS score in the botulinum toxin A group was reduced from 8.1 to 2.5 ($p < 0.001$). Side effects for both therapies were few and subsided with treatment with general antibiotics and nonsteroidal antiinflammatory drugs.

Conclusions: Gabapentin and botulinum toxin A are safe and effective treatments for vulvodynia. This condition can cause sexual dysfunction and affect quality of life. However, with proper management, satisfactory outcomes for women with vulvodynia can be achieved.

Keywords: *Dyspareunia; Gabapentin; Type A botulinum toxins; Vulvodynia*

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INTRODUCTION

Vulvodynia is a condition in women that is characterized by chronic vulvar pain. It may be present constantly, intermittently, or only with intromission during sexual intercourse. The term *vulvodynia* was originally coined by McKay [1], and it has been adopted by the International Society for the Study of Vulvar Disease Task Force to describe any vulvar pain [2]. There are no standardized classifications for vulvodynia largely because it is a multifactorial condition in which certain subsets coexist within others. Generalized vulvodynia, or essential vulvodynia, usually occurs in postmenopausal or perimenopausal women and is exhibited by diffuse, unremitting, and burning pain that is not cyclic [1-4]. This pain may occur in different areas of the vulva at different times, and it may be constant or occur only every once in a while. Vulvar vestibulitis syndrome is specifically characterized by pain in the vestibule and usually occurs in premenopausal women. In this condition, pain occurs with vaginal entry by the penis or a tampon [1,2].

Patients with vulvodynia usually describe their pain as a chronic burning in the vulvovestibular area that typically lasts more than 3 months. Before a diagnosis of vulvodynia is made, other vulvovaginal problems should be ruled out [3,4]. Vulvodynia not only causes pain, but often leads to sexual dysfunction, including arousal and orgasmic difficulty [3,4]. For many women, it reduces overall personal health and quality of life.

The etiology of vulvodynia is not clear, and because of

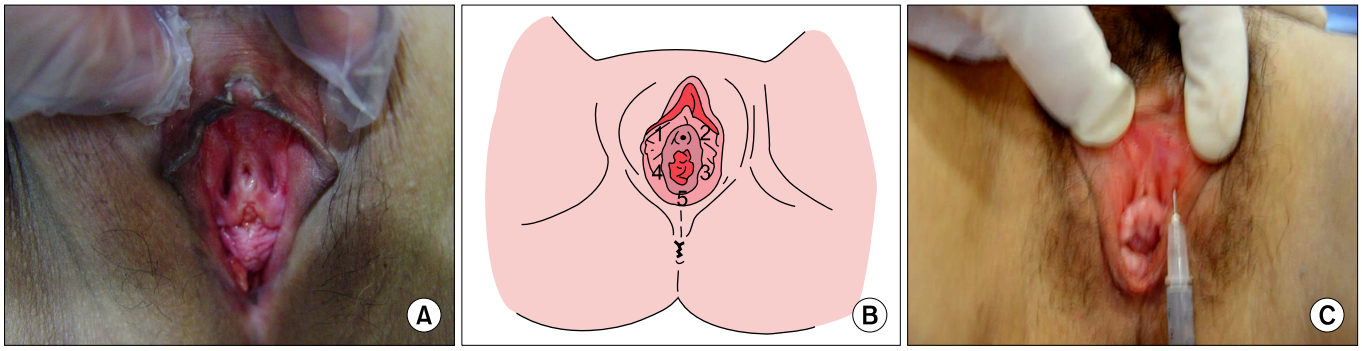

FIG. 1. The process of pain mapping and intralesional botulinum toxin A injection. (A) Using the Q-tip test, all painful areas were checked for intensity and localization. (B) Pain was scored by use of a visual analogue scale and mapped. (C) Botulinum toxin A was injected on the basis of the pain map (20 IU in each site, up to a maximal total dose of 100 IU).

this, many patients do not receive optimal treatment. The most common type of vulvodynia is vulvar vestibulitis syndrome, which usually has an acute onset [5]. Vulvodynia is generally associated with vaginitis, changes in sexual activity, and a history of medical procedures on the vulva such as cryotherapy or laser treatment (after which it often becomes a chronic problem). With vulvodynia in general, vulvar pain is variable in intensity, from mild to disabling. Patients may feel burning, stinging, rawness, aching, soreness, or throbbing that occurs in the vulva, labia, or vagina. A large proportion of patients attend multiple medical consultations before receiving a diagnosis, and no single treatment or combination of treatments have been shown to consistently improve the symptoms. Recently, gabapentin a γ-aminobutyric acid (GABA) analogue anticonvulsant and botulinum toxin A have been shown to be effective in treating vulvodynia [3,6]. In this study, we performed a retrospective analysis of the clinical characteristics and the outcomes of these 2 drugs in the treatment of patients with vulvodynia.

MATERIALS AND METHODS

This study was conducted by use of data from 73 patients presenting with sexual dysfunction and vulvodynia out of 164 total women with vulvar pain who visited our clinic from 2002 to 2010. We reviewed the patients' medical histories and noted the type of drugs administered for pain treatment and the duration of treatment. We also performed physical examinations, including a vaginal examination and vulvovaginal pain mapping with a cotton tip, to determine the location and degree of pain and to rule out other treatable causes of vulvar pain, such as infections of the vagina or uterus and genitourinary benign or malignant tumors. Vulvodynia was diagnosed if the patient had no other causes of vulvar pain that occurred either only during sexual activity or constantly. To rule out other painful, treatable, vulvar diseases, the patients' previous and current medical histories and medications were reviewed and urinalysis, urine culture with sensitivity test, papanicolaou test smears, and basic hematological tests were performed on all 164 vulvar pain patients. Patients with abnormal test results suggesting definitive infection, benign tumor, or painful bladder syndrome were excluded, resulting in 73 patients with a diagnosis of vulvodynia of unknown etiology.

Using the Q-tip test, a cotton-tip was used to confirm pain in the vulvovestibular area and to measure its intensity and localization (Fig. 1A, B). The patient's objective pain intensity was evaluated by use of a visual analogue scale (VAS) and was scored from 0 to 10. All pain characteristics were self-recorded by the patient on a questionnaire. Patient data were analyzed according to treatment (either botulinum toxin A injection or gabapentin oral medication), treatment response, treatment duration, side effects, and pre- and posttreatment changes in VAS score. The method of vulvodynia treatment was selected according to patient preference or response to previous treatment. Gabapentin was prescribed to the patients who preferred to take oral medication, with an initial dose of 300 mg per day that was flexibly increased depending on response. Gabapentin administration was intended for at least 2 months, although the actual duration depended on patient willingness and response.

Intralesional injection of botulinum toxin A (Botox, Allegran Inc., Irvine, CA, USA) was used for patients who preferred an injectable treatment and for those experiencing no pain relief from gabapentin oral treatment after more than 3 months. For treatment with botulinum toxin A, the entire vulvovestibular pain area was mapped with a Q-tip. The drug was injected into the submucosal layer at each painful area, after the pain in that area was reconfirmed (Fig. 1B, C). The dose of botulinum toxin A at each injection site was 20 IU, and the total number of injection sites was limited to 5. The minimum total dose was 40 IU and the maximum dose was 100 IU. Two weeks after the injection, a telephone interview was conducted to check for any adverse reactions. If significant pain persisted at any area of the vulvar vestibule at the 4-week follow-up, additional injections were administered by use of the same method. After the second round of injections, no further treatments were administered. Side effects, adverse re-

TABLE 1. Patient ages and treatment characteristics

Characteristic	Gabapentin	Botulinum toxin A
No. of patients	62	11
Age (y), mean±SD (range)	45.7±9.0 (31–65)	39.9±9.5 (25–55)
Treatment duration (mo)	2.3±1.8 (0.5–6)	NA Follow-up, 12.7 (6–24)
Dose, mean (range)	329.03 mg/d (300–900 mg/d)	59.1 IU (40–100 IU; median, 50 IU)
Side effect	Nausea (6.5%, 4/62) Drowsy (9.7%, 6/62)	Temporary pain on injection site (18.2%, 2/11)

SD, standard deviation.

actions, and treatment outcomes were assessed at 4 and 8 weeks after the initial injections. Every 2 months after the final round of injections, change in pain level and total dose received were recorded.

All procedures were performed in an outpatient clinic with informed consent. To prevent infection, prophylactic antibiotics were prescribed. To compare changes in pre- and posttreatment VAS scores, data were analyzed by use of a paired t-test with statistical significance set at $p < 0.05$.

RESULTS

Seventy-three patients with vulvodynia were analyzed for this study, 6 of whom reported being unable to have sexual intercourse as the result of severe vulvar pain. Sixty-two patients (mean age, 45.7±9.0 years; range, 31 to 65 years) were treated with gabapentin and 11 (mean age, 39.9±9.5 years; range, 25 to 55 years) were treated with botulinum toxin A (Table 1). Four (6.5%) of the 62 women treated with gabapentin later converted to botulinum toxin A treatment owing to unsatisfactory improvement after more than 2 months of gabapentin treatment (600 mg in 2 patients, 300 mg in 2 patients). The mean duration of gabapentin treatment was 2.3±1.8 (range, 0.5 to 6 months) months, and the mean dose was 329.0 mg/d (range, 300 to 900 mg/d). The effective dose was 600 mg for 4 patients (6.5%), 900 mg for 1 patient (1.6%), and 300 mg for the remaining 57 patients (91.9%). The mean duration of botulinum toxin A treatment was 12.7 months (range, 6 to 24 months), and the mean effective dose was 59.1 IU (range, 40 to 100 IU). The effective dose of botulinum toxin A was 40 IU for 2 patients (18.1%), 70 IU for 1 patient (9.1%), and 100 IU for 8 patients (72.7%). Five patients received 2 rounds of injections: 2 of these received 20 IU initially and 20 IU at week 4 (total 40 IU), 1 received 40 IU initially and 30 IU at week 4 (total 70 IU), and 2 received 40 IU initially and 60 IU at week 4 (total 100 IU). The other 6 patients had only initial injections, all at a total dose of 100 IU.

Pretreatment VAS scores were 8.6 (range, 6 to 10) for the gabapentin treatment group and 8.1 (range, 5 to 10) for the botulinum toxin A treatment group. Posttreatment VAS scores were significantly reduced for each group: 3.2 (range, 1 to 8) for the gabapentin group and 2.5 (range, 0 to 5) for the botulinum toxin A group ($p < 0.001$) (Fig. 2).

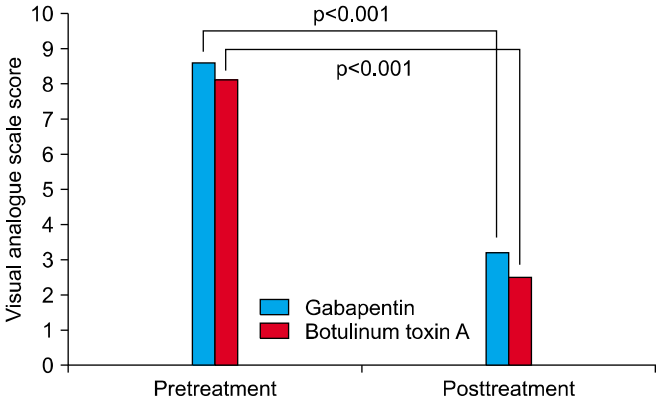

FIG. 2. Pre- and posttreatment changes in visual analogue scale scores for the gabapentin and botulinum toxin A treatment groups.

A total of 50 (80.6%) of 62 patients in the gabapentin treatment group were satisfied with the treatment, and 8 (72.7%) of 11 patients in the botulinum toxin treatment group were satisfied with the treatment. All four patients who converted from gabapentin to botulinum toxin injection were satisfied with the result after the injection. In the gabapentin group, 4 patients (6.5%) experienced nausea and 6 (9.7%) experienced drowsiness, but there were no cases of drug withdrawal. Two patients in the botulinum toxin A group (18.2%) felt a burning sensation with transient pain at the injection sites, but these symptoms were resolved with conservative treatment without any significant sequelae.

DISCUSSION

Vulvodynia is a chronic vulvar pain syndrome, the cause and visible pathology of which remain unclear. Patients with vulvodynia usually describe their pain as a chronic burning occurring in the vulvovestibular area that typically lasts longer than 3 months [3]. The vulvovestibular areas of these patients appear normal, and therefore the syndrome is often misdiagnosed as psychosomatization or female urethral syndrome. In 1988, the International Society for the Study of Vulvovaginal Disease adopted the term *vulvodynia* with the following classifications: vulvar

dermatoses, cyclical vulvitis (or cyclical candidiasis), vulvar vestibulitis, vulvar papillomatosis, and essential (or dysaesthetic) vulvodynia [7]. Although this classification is currently not often used, it may be generally applied to patients who have chronic pain or burning lasting for 3 months and with no obvious visible lesions [3]. For women with sexual dysfunction, the clinical diagnosis of vulvodynia is generally limited to essential vulvodynia without any obvious etiology.

Pain is a complex sensation involving sensory-discriminative, affective-motivational, and cognitive-evaluative aspects. A recent theory on the cause of vulvodynia suggests that neurogenic inflammation and the accompanying pain are chronic sequelae of central and peripheral sensitization resulting from the bidirectional influence of peripheral inflammation and the nervous system [8-10]. Gabapentin a GABA analogue anticonvulsant possesses both antiepileptic and antinociceptive effects. It is used to treat sympathetic dystrophy, trigeminal neuralgia, postherpetic neuralgia, diabetic neuropathy, migraine, acute pain in herpes zoster infection, and other types of neuropathic pain [6]. Although its mechanism of action is unclear, several possibilities have been suggested, including 1) selective activation of the heterodimeric GABA (B) receptor subunits GABA (B1a) and GABA (B2), 2) selective enhancement of the N-methyl-D-aspartate current at GABAergic interneurons, 3) blockage of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-receptor-mediated transmission in the spinal cord, 4) binding to the L-alpha-amino acid transporter, 5) activation of adenosine triphosphate-sensitive K(+) channels, 6) activation of hyperpolarization-activated cation channels, and 7) modulation of Ca(2+) current by selective binding to the specific binding site of [^{3}H]gabapentin (the alpha 2/delta subunit of voltage-dependent Ca(2+) channels) [6]. Gabapentin is believed to have different mechanisms of action for different therapeutic effects.

Several studies have shown that gabapentin administration yields significant results in the treatment of vulvodynia, with more than 80% of patients reported to experience symptom improvement [11-14]. Boardman et al. [11] found this treatment to reduce vulvar pain from a VAS score of 7.26 to a score of 2.49. In our study, gabapentin produced similar antinociceptive outcomes, reducing VAS scores from 8.6 to 3.2 ($p < 0.001$). However, the mechanism of action by which gabapentin relieves chronic vulvodynia is not entirely clear. The neuromatrix theory suggests that pain is a multidimensional experience induced by characteristic nerve impulse neurosignature patterns generated by the body-self neuromatrix in the brain [8]. The concept of central sensitization of peripheral neurogenic inflammation suggests that gabapentin inhibits afferent pain pathways to the central nervous system, thereby reducing pain perception in the vulvovestibular area [8,15,16]. The benefits of gabapentin include few side effects and minimal interactions with other medications. Ness et al. [17] reported on its use in 260 patients experiencing chronic pain of multiple etiologies and found that only 14% quit the trial as a result of negative side effects, which primarily included drowsiness, confusion, dizziness, imbalance, and nausea. Seventy-three percent of the patients in that study experienced less pain as a result of treatment and, of those, 54% achieved long-term benefit. Of those patients suffering from peripheral neuropathic pain, 87% improved with gabapentin treatment.

Similar to that report, in our study, there were only mild side effects and satisfactory pain relief was achieved for the majority of patients. In 91.9% of patients, the effective dose of gabapentin was 300 mg. Some of the patients in the 300 mg and 600 mg treatment groups converted to botulinum toxin A treatment owing to unsatisfactory results, but not because of drug side effects. Therefore, our results suggest that gabapentin can be safely and effectively used in vulvodynia patients. One of the benefits of gabapentin is that the dosage can be adjusted depending on patient response. Although most of our patients noted improvements at 300 mg, some patients who were not satisfied after more than 2 months of treatment at this dose received increased doses and experienced improvement at doses of 600 mg or 900 mg gabapentin. This suggests that clinicians should determine the optimal treatment dose on the basis of the patient's specific pain tolerance.

Botulinum toxin is a natural neurotoxin derived from the Gram-positive anaerobic bacterium *Clostridium botulinum* [18]. It binds to the synaptic cholinergic terminals of a neuromuscular junction and inhibits acetylcholine release. The affected nerve terminals do not degenerate; thus, neural function recovers through axonal sprouting and the formation of new synaptic contacts [19]. The autonomic effects of botulinum toxin are based on the blocking of acetylcholine release in all parasympathetic and post-ganglionic sympathetic neurons. The time necessary to recover function from paralysis depends on the types of toxin and the nerve terminal; it usually takes 2 to 4 months at the mammalian neuromuscular junction and occasionally up to 1 year or more in autonomic neurons [20]. The peripheral antinociceptive effects of botulinum toxin A have been indicated in the treatment of various diseases, and its potential indications are growing. Chronic pain diseases such as bladder pain syndrome, interstitial cystitis, and chronic pelvic pain syndrome have all shown effective relief through botulinum toxin A injections [21-23]. In those studies, botulinum toxin A treatment resulted in marked improvements in patients with intractable pain that could not be controlled with other conventional pain management approaches [21-23].

There have been few studies on botulinum toxin A treatment for vulvodynia. Our results suggest that for vulvodynia without pelvic floor muscle spasms, the effects of botulinum toxin A may be the result of neuronal uptake of the toxin or its metabolites, with subsequent influence on peripheral or central nociceptors. The induced alterations in the neurosecretion of neurotransmitters and neuropeptides may also contribute to pain relief. In our study, botu-

linum toxin A produced significant reductions in pain without short-term recurrence. The antinociceptive action of botulinum toxin A is known to last for approximately 1 year and usually appears within 1 to 2 months after injection. Therefore, our protocol was to follow up at the fourth week to check for unimproved lesions and to administer additional injections. After the second round of injections, pain was assessed. The majority of patients received more than 40 IU, and the patients receiving 100 IU at the initial treatment did not receive additional doses during the follow-up. This suggests that an initial maximal dose would be a more effective approach to pain relief with botulinum toxin A. However, this should be investigated in future studies. In our previous study on a small number of patients, botulinum toxin A was effective at relatively large doses, whereas doses less than 20 IU showed no significant effect compared with placebo [4,24,25]. An optimal dose therefore remains to be determined. It should also be noted that, to achieve successful botulinum toxin A treatment of vulvodynia, it is important to correctly identify the localization of pain in the vulvovestibular area.

This study had several limitations. Although the treatment protocol was universal for all patients, the study was not controlled because it was performed retrospectively through chart review. In addition, the treatment dose was not fixed. Therefore, we need to perform further studies comparing treatment efficacy between each drug as well as with placebo. Nonetheless, in this study, we have ascertained effective clinical management strategies for vulvodynia.

CONCLUSIONS

Gabapentin and botulinum toxin A are both safe and effective treatments for vulvodynia that lead to significant reductions in pain. The improvements in patient outcomes that we found suggest that vulvodynia has physiological, and possibly neuropathic, bases. This condition can negatively impact quality of life, but with proper management, satisfactory pain relief is achievable. Urologists should therefore be attentive to this condition and consider these promising treatment options.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. McKay M. Vulvodynia. A multifactorial clinical problem. Arch Dermatol 1989;125:256-62.
2. International Society for the Study of Vulvar Disease Taskforce. Burning vulvar syndrome: report of the ISSVD taskforce. J Reprod Med 1984;29:457.
3. Lotery HE, McClure N, Galask RP. Vulvodynia. Lancet 2004; 363:1058-60.
4. Yoon H, Chung WS, Shim BS. Botulinum toxin A for the management of vulvodynia. Int J Impot Res 2007;19:84-7.
5. Bergeron S, Binik YM, Khalife S, Meana M, Berkley KJ, Pagidas K. Treatment of vulvar vestibulitis syndrome: toward a mutilmodal approach. Sex Marital Ther 1997;12:305-11.
6. Cheng JK, Chiou LC. Mechanisms of the antinociceptive action of gabapentin. J Pharmacol Sci 2006;100:471-86.
7. McKay M. Subsets of vulvodynia. J Reprod Med 1988;33:695-8.
8. van Lankveld JJ, Granot M, Weijmar Schultz WC, Binik YM, Wesselmann U, Pukall CF, et al. Women's sexual pain disorders. J Sex Med 2010;7(1 Pt 2):615-31.
9. Steers WD, Tuttle JB. Neurogenic inflammation and nerve growth factor: possible roles in interstitial cystitis. In: Sant GR, editor. Interstitial cystitis. Philadelphia: Lippincott-Raven Publishers; 1997. p. 67-75.
10. Wesselmann U. Neurogenic inflammation and chronic pelvic pain. World J Urol 2001;19:180-5.
11. Boardman LA, Cooper AS, Blais LR, Raker CA. Topical gabapentin in the treatment of localized and generalized vulvodynia. Obstet Gynecol 2008;112:579-85.
12. Ventolini G, Barhan S, Duke J. Vulvodynia, a step-wise therapeutic prospective cohort study. J Obstet Gynaecol 2009;29: 648-50.
13. Harris G, Horowitz B, Borgida A. Evaluation of gabapentin in the treatment of generalized vulvodynia, unprovoked. J Reprod Med 2007;52:103-6.
14. Ben-David B, Friedman M. Gabapentin therapy for vulvodynia. Anesth Analg 1999;89:1459-60.
15. Yoshimura N, de Groat WC. Increased excitability of afferent neurons innervating rat urinary bladder after chronic bladder inflammation. J Neurosci 1999;19:4644-53.
16. Fitzgerald MP, Koch D, Senka J. Visceral and cutaneous sensory testing in patients with painful bladder syndrome. Neurourol Urodyn 2005;24:627-32.
17. Ness TJ, Crimaldi JC, McDanal JT. Case report on gabapentin. Reg Anesth Pain Med 1998;23:110-1.
18. Simpson LL. Molecular pharmacology of botulinum toxin and tetanus toxin. Annu Rev Pharmacol Toxicol 1986;26:427-53.
19. Angaut-Petit D, Molgo J, Comella JX, Faille L, Tabti N. Terminal sprouting in mouse neuromuscular junctions poisoned with botulinum type A toxin: morphological and electrophysiological features. Neuroscience 1990;37:799-808.
20. Naumann M, Jost WH, Toyka KV. Botulinum toxin in the treatment of neurological disorders of the autonomic nervous system. Arch Neurol 1999;56:914-6.
21. Gottsch HP, Yang CC, Berger RE. A pilot study of botulinum toxin A for male chronic pelvic pain syndrome. Scand J Urol Nephrol 2011;45:72-6.
22. Gottsch HP, Yang CC, Berger RE. A review of botulinum toxin use for chronic pelvic pain syndrome. Curr Urol Rep 2010;11:265-70.
23. Giannantoni A, Cagini R, Del Zingaro M, Proietti S, Quartesan R, Porena M, et al. Botulinum A toxin intravesical injections for painful bladder syndrome: impact upon pain, psychological functioning and Quality of Life. Curr Drug Deliv 2010;7:442-6.
24. Petersen CD, Giraldi A, Lundvall L, 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;6:2523-37.
25. Pelletier F, Parratte B, Penz S, Moreno JP, Aubin F, Humbert P. Efficacy of high doses of botulinum toxin A for treating provoked vestibulodynia. Br J Dermatol 2011;164:617-22.