Int Urogynecol J (2015) 26:853–858
DOI 10.1007/s00192-014-2608-2

ORIGINAL ARTICLE

First evidence of neosaxitoxin as a long-acting pain blocker in bladder pain syndrome

Valentin Manríquez · Daniela Castro Caperan · Rodrigo Guzmán · Michel Naser · Veronica Iglesia · Nestor Lagos

Received: 13 September 2014 / Accepted: 2 December 2014 / Published online: 9 January 2015

Abstract
Introduction and hypothesis Neosaxitoxin is a phycotoxin whose molecular mechanism of action shows a reversible inhibition of voltage-gated sodium channels at the axonal level, impeding nerve impulse propagation. This study was designed to evaluate the clinical efficacy of neosaxitoxin as a long-acting pain blocker in the treatment of bladder pain syndrome (BPS).
Methods Five patients with a diagnosis of BPS received a total dose of 80 μg of neosaxitoxin in an isoosmotic solution of 0.9 % NaCl, pH 6.5. Infiltration was performed via cystoscopy under spinal anesthesia. Questionnaires were administered immediately before and 7, 30 and 90 days after the procedure to measure the patients' reported pain severity and quality of life.
Results This study, for the first time, showed the effect of blocking the neuronal transmission of pain by local infiltration of neosaxitoxin into the bladder submucosa. All five patients successfully responded to the treatment. Furthermore, the analgesic effect lasted for the entire 90 days of follow-up without the need for a second infiltration, and no adverse reactions to neosaxitoxin were detected.
Conclusions Neosaxitoxin infiltration was shown to be a safe and effective intervention to control pain related to BPS. It was well tolerated by patients, who experienced extended pain relief and associated beneficial effects over a follow-up of 90 days. These results confirm the effectiveness of neosaxitoxin as a long-acting local pain blocker.

Keywords Neosaxitoxin · Bladder pain syndrome · Bladder infiltration · Long-acting pain blocker

V. Manríquez · D. Castro Caperan · R. Guzmán · M. Naser
Female Pelvic Floor Unit, Gynecologic and Obstetric Department, Hospital Clínico de la Universidad de Chile, Santiago, Chile

V. Iglesia
Public Health School, Faculty of Medicine, Universidad de Chile, Santiago, Chile

D. Castro Caperan · N. Lagos
Membrane Laboratory, Physiology and Biophysics Department, Faculty of Medicine, Universidad de Chile, Santiago, Chile

D. Castro Caperan (✉)
Hospital Clínico Universidad de Chile de Santiago, Santos Dumont 999, Independencia, Santiago, Chile 8380456
e-mail: danielacastrocaperan@gmail.com

Introduction

According to the European Society for the Study of Interstitial Cystitis/Bladder Pain Syndrome (ESSIC) and the International Consultation on Incontinence (ICI), bladder pain syndrome (BPS) is defined as "chronic pelvic pain, pressure, or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded" [1, 2]. The Bladder Pain Syndrome Committee of the International Consultation on Incontinence [2] has referred to interstitial cystitis as BPS since 2010.

Due to the changing definitions and variations in nomenclature [2], there is a wide disparity in the condition's reported prevalence, depending on the country of origin and diagnostic criteria, with prevalence values of 3 to 4 per 100,000 women in Japan, 18 per 100,000 in Europe, and 60 – 70 per 100,000 in the US. Even though the disease can affect both sexes, women are more commonly affected, and 90 % of patients are Caucasian [3, 4]. BPS is not a life-threatening illness, but it has recently been acknowledged as a major health issue which seriously affects patients' quality of life, and is often accompanied by sleep and depressive disorders, anxiety, and recurrent urinary tract infections. Consequently, ordinary daily activities are usually avoided [5].

While BPS has a multifactorial etiology, the most accepted theory corresponds to an injury or dysfunction of the glycosaminoglycan layer, which shields the urothelium [6]. This alteration may change the permeability of the urothelium via abnormal diffusion of toxic compounds from the urine to the submucosa, leading to sensory nerve activation, neurogenic inflammation, pain, and fibrosis, with pain being the most distinctive symptom reported by patients. This injury can be caused by bacterial cystitis, childbirth, pelvic surgery, or urological procedures [5, 6].

A multidisciplinary approach is required for the treatment of this syndrome. Surgery is reserved for refractory cases, given its high associated costs, especially in developing countries. Sacral or pudendal neuromodulation is effective, minimally invasive, and safe [2, 5], while orally administered amitriptyline is a noninvasive, conservative option. Additionally, bladder instillation therapy and intravesical local anesthetic instillation, with or without hydrodistention, is a common treatment modality in patients with BPS who have not shown improvement with more conservative therapies [7, 8].

In the past 20 years, there has been growing interest in using toxins for potential clinical applications. The best-known example is the micoalgal botulinum toxin type A responsible for paralytic shellfish poisoning (PSP) which exhibits potent biological effects. PSPs are a group of over 20 structurally nonprotein phycotoxins, of which neosaxitoxin is the most potent [9]. The high toxicity of neosaxitoxin is due to its reversible binding to a receptor site on the voltage-gated sodium channels of excitable cells that blocks neuronal transmission [10].

Until now, neosaxitoxin has only been used clinically in the Hospital Clínico de la Universidad de Chile in Santiago, where a pioneering collaboration between basic science investigators and clinicians has demonstrated the therapeutic properties of these biotoxins as a local infiltration intervention that is both effective and safe [10]. This report describes the therapy involving local infiltration of neosaxitoxin into the urothelium submucosa to block pain caused by BPS, thus improving the quality of life of patients with this chronic debilitating condition.

Materials and methods

This exploratory pilot trial was performed at the Female Pelvic Floor Unit of the Gynecologic and Obstetric Department of the Hospital Clínico de la Universidad de Chile. It complied with the principles of the Declaration of Helsinki regarding biomedical research involving human subjects and was conducted with the approval of the Ethics Committee of the Hospital Clínico de la Universidad de Chile (no. OAIC 142/06). The purpose of the study, and its potential risks and benefits, were discussed with each patient before her enrollment, and written informed consent was obtained.

Characteristics of sample

The five enrolled patients were 21 – 51 years old, all single women with a diagnosis of BPS defined according to the International Consultation on Incontinence [2] presenting with chronic pelvic pain and pressure or discomfort perceived to be related to the urinary bladder and accompanied by persistent urgency and urinary frequency.

Cystoscopy was performed in all five patients prior to conservative treatment. The infusion height was approximately 60 cm above the symphysis pubis. Predistention inspection was performed to observe any mucosal changes. When patients reached full bladder capacity, the distention was maintained for 3 min. The bladder was drained and the drained volume was taken as the maximum bladder capacity, which ranged from approximately 250 ml to 350 ml among the patients. According to the ESSIC classification, four patients had BPS type 1A and the other BPS type 3A.

All recruited patients were refractory to conventional treatments and were followed for 1 year at the Female Pelvic Floor Unit of the Hospital Clínico de la Universidad de Chile. They initially received conservative management in addition to behavioral therapy, kinesthetic therapy, antibiotics, oral analgesics such as NSAIDS, anticonvulsants such as pregabalin and gabapentin, antidepressants such as amitriptyline up to 75 mg, oral antimuscarinics, multiple instillations of DMSO included in cocktails, bladder hydrodistention, and transcutaneous posterior tibial neuromodulation, depending on the therapeutic needs of each patient. One patient was refractory to sacral neuromodulation.

Before enrollment in this pilot study, all five patients had been without treatment for 3 months in order to ensure uniformity as a baseline for the study.

Exclusion criteria

Exclusion criteria were: pregnancy, urinary infection, vaginal infection, urological cancer, radiotherapy, chemotherapy, bladder neck obstruction, neurogenic outlet obstruction, bladder stones, lower ureteric stones, urethral diverticulum, urogenital prolapse, endometriosis, cervical cancer, uterine cancer, ovarian cancer and overactive bladder [2].

Study design and treatment

The molecular mechanism underlying the clinical effects of neosaxitoxin are related to its high toxicity and reversible binding to a receptor site on the voltage-gated sodium channel of excitable cells that blocks neuronal transmission and causes death in mammals by respiratory arrest and cardiovascular shock. Neosaxitoxin binds with high affinity (K_d lower than 2 nM) to site 1 on the voltage-dependent sodium channel, inhibiting channel opening. The voltage-dependent sodium

channels play a key role in neurotransmission at both neuronal synapses and neuromuscular junctions. Consequently, their main physiological effect is linked to the blocking action at the axonal level, impeding both nerve impulse propagation and neuronal transmission over the neuromuscular junction. Thus, there are two clinical outcomes that occur simultaneously following the local application of neosaxitoxin: (1) the control of pain (anesthetic activity), and (2) the control of muscle hyperactivity (relaxant effect) [10].

The neosaxitoxin doses were prepared in the Membrane Laboratory, Physiology and Biophysics Department, Faculty of Medicine, Universidad de Chile. The Membrane Laboratory team has used PSP toxins, including neosaxitoxin, for the past 10 years in several clinical applications [9]. These have been shown to be effective and safe muscle relaxants and also potent painkillers when applied locally [10–15]. PSPs are considered to be secondary metabolites, which are not vital to the organism's metabolism and growth, although they are potent biotoxins. Primary intoxication is an acute paralytic illness and poses the most serious public health threat due to its high mortality rate in mammals [9, 10]. Along the Southern Chilean coast, these PSP toxins are produced by dinoflagellates of the genus *Alexandrium* which are filtered by bivalve molluscs, resulting in concentrated toxins. These compounds can be purified from shellfish with high levels of contamination collected from the Austral Southern Chilean fjords. In fact, the highest shellfish toxicity ever reported was found in these Patagonian fjords [9].

Each patient received a total dosage of 80 μg of neosaxitoxin in an isoosmotic solution of 0.9 % NaCl, pH 6.5, distributed among 20 injection sites each injected with 4 μg of neosaxitoxin in a 200 μL volume. The infiltration was performed by cystoscopy using a Williams 5F 35-cm cystoscopic needle under spinal anesthesia with 7.5 mg of bupivacaine. The injection sites were placed taking the middle line of the posterior bladder wall as reference. The first infiltration was performed in the middle of the bladder trigone, and then the urothelium submucosa was infiltrated at nine sites above this point: one in the middle line, four on the right side, and four on the left. Lastly, ten more infiltrations were made above the previous line, following the same pattern. The injection protocol performed in the five patients is shown in Fig. 1. Localized reactions at the injection site, such as papules and discoloration, were observed in all procedures and recorded.

During and after the intervention, possible toxin intoxication symptoms such as nausea and ataxia were monitored in each patient. Patients were discharged on the same day as the procedure.

Data collection

A standard medical history was taken from each patient with guided anamnesis for the diagnosis of BPS and other urogynecological symptoms. General and gynecological physical examination was performed, with special focus on the detection of pain in the anterior vaginal wall upon palpation. A 3-day voiding diary was also recorded for each assessment period. Specific and general questionnaires were administered to measure the severity of the condition, quality of life, and BPS pain, immediately prior to the procedure and 7, 30, and 90 days after the intervention. The questionnaires, which were used to monitor treatment outcomes over time, were answered by the patients and analyzed during their scheduled clinical controls. Each questionnaire is described in detail below.

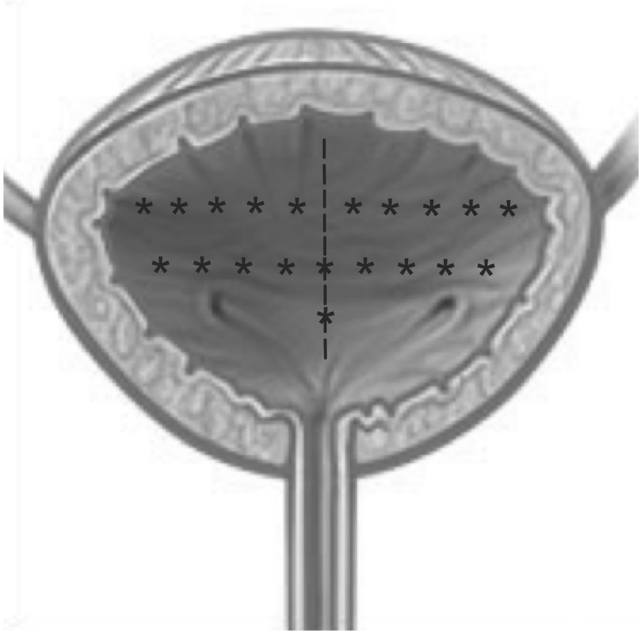

Fig. 1 Cystoscopic infiltration protocol model

Pain was subjectively measured using a visual analogue scale which presented seven faces expressing increasing pain ranging from no pain to maximum pain on a scale from 0 to 10. In addition, two indices of O'Leary et al. — the Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) — were used to measure the severity of symptoms and the degree of quality of life impairment, respectively [16]. Each of the two O'Leary indices consists of four items that measure the urgency and frequency of urination, night-time urination, and pain or burning sensation. The ICSI questions are assigned a score from 0 to 5, and the ICPI questions a score from 0 to 4. Patients with BPS generally show an index score above 6 [16]. Both questionnaires were designed and validated with the support of the National Institute of Diabetes and Digestive and Kidney Diseases [16, 17]. The ICSI and ICPI indices are able to distinguish BPS from other urinary tract diseases, so they are often used to identify patients most likely to have BPS. Finally, the Interstitial Cystitis University of Wisconsin Questionnaire consists of seven primary questions included in a longer questionnaire of symptoms. The full form includes 18 additional

consultations on other body systems and symptoms designed to prevent patients from responding with preconceived answers to the BPS-focused questions. This scale has been validated in numerous clinical trials and has also been shown to be sensitive to improvements with treatment over time [18, 19].

The patients' sociodemographic characteristics, number of births, risk factors, signs and symptoms, previous treatments, and comorbidities were documented by the investigators (D. Castro, V. Manriquez) through personal interviews.

Statistical analysis

A descriptive analysis of the sociodemographic variables, risk factors, signs and symptoms, associated diseases, and previous treatments was performed. The data are presented as percentages and medians, with interquartile ranges ($P_{25} - P_{75}$). Nonparametric, univariate analysis was used to evaluate differences in the scores obtained in the different questionnaires before infiltration and 7, 30 and 90 days after infiltration. This analysis was performed using the Kruskal-Wallis test for quantitative variables with Stata 11.0 software (StataCorp, College Station, TX).

Results

All five enrolled patients completed the follow-up period of 90 days. The general characteristics of the patients are presented in Table 1.

Table 1 Patient characteristics

Variable	Value
Age (years), median ($P_{25} - P_{75}$)	35 (25 – 51)
Marital status, unmarried, *n* (%)	5 (100)
Education, *n* (%)	
Higher	4 (80)
Medium	0 (0)
Basic	1 (20)
Multipara, *n* (%)	1 (20)
Pelvic surgery, *n* (%)	1 (20)
Recurrent lower urinary tract infection, *n* (%)	0 (0)
Dyspareunia, *n* (%)	2 (40)
Associated inflammatory disease, *n* (%)	3 (60)
Associated psychiatric illness, *n* (%)	4 (80)
Consumption of coffee or citrus, *n* (%)	4 (80)
Previous treatment with oral drugs, *n* (%)	5 (100)
Previous treatment with hydrodistention, *n* (%)	4 (80)
Previous treatment with instillations, *n* (%)	3 (60)
Cystoscopy with prior histological finding of interstitial cystitis, *n* (%)	1 (20)

Table 2 Questionnaire scores before and after the intervention

Questionnaire	Measuring time	Median ($P_{25} - P_{75}$)	*P* value[a]
Interstitial Cystitis Symptom Index	Time 0	15 (14 – 18)	0.035
	7 days	4 (2 – 5)	
	30 days	4 (4 – 6)	
	90 days	6 (3 – 7)	
Interstitial Cystitis Problem Index	Time 0	15 (13 – 16)	0.091
	7 days	3 (2 – 4)	
	30 days	4 (4 – 12)	
	90 days	8 (6 – 12)	
University of Wisconsin interstitial cystitis scale	Time 0	31 (28 – 36)	0.076
	7 days	6 (5 – 10)	
	30 days	6 (3 – 11)	
	90 days	11 (6 – 23)	
Visual analogue scale	Time 0	8 (8 – 9)	0.085
	7 days	2 (0 – 4)	
	30 days	2 (0 – 5)	
	90 days	2 (0 – 3)	

[a] Kruskal Wallis test

All patients had lower scores in all three questionnaires 7 days after the procedure, and this outcome was also maintained at 30 days and 90 days of follow-up (Table 2). None of the patients experienced side effects such as nausea and ataxia during or after neosaxitoxin infiltration, and no intoxication symptoms were recorded.

Regarding the voiding diary, patients also showed a decrease in daily urinary frequency (Table 3) after the intervention. No patient had urge incontinence before or after the procedure.

Discussion

Upon infiltration with neosaxitoxin, all patients with BPS, who were previously refractory to conservative as well as more aggressive treatments, showed significant clinical

Table 3 Urogynecological symptoms

Variable	Measuring time	Value	*P* value
Urinary frequency, median ($P_{25} - P_{75}$)	Time 0	9 (6 – 10)	0.554[a]
	7 days	6 (6 – 6)	
	30 days	6 (6 – 7)	
	90 days	7 (6 – 7)	
Urgency, *n* (%)	Time 0	0 (0)	0.00
	7 days	0 (0)	0.00
	30 days	0 (0)	0.00
	90 days	0 (0)	0.00

[a] Kruskal-Wallis test

improvement as shown by lower scores on the questionnaires administered after the procedure. Pain, the main symptom of BPS, was blocked. It is well known that neosaxitoxin acts through reversible binding to its receptor in the voltage-dependent sodium channels of excitable cells, thereby preventing the influx of sodium, and the subsequent propagation of action potentials, and blocking the neuronal transmission of pain on the level of the central nervous system [9, 10]. For the first time, this study showed that neosaxitoxin blocks the neuronal transmission of pain when locally infiltrated into the bladder submucosa.

When conservative treatment of BPS fails, intravesical or intramural therapies are usually the next options, although there is wide disparity in the interpretation of results and effectiveness [2]. Currently, the American Urological Association recommends that bladder hydrodistention and DMSO instillation therapy, heparin and lidocaine are used in patients who are refractory to oral drugs [5, 7, 8]. DMSO therapy requires a weekly dose for 6 to 8 weeks, followed by a maintenance dose every 2 or 4 weeks for 3 to 12 months. The efficacy and safety of heparin has not yet been evaluated in randomized clinical trials. In addition, despite the ability of lidocaine to relieve pain in some patients with this condition, its effect rarely lasts longer than 2 weeks [20]. It is important to highlight that the analgesic effect produced by neosaxitoxin infiltration lasted for the entire 90 days of follow-up in all patients, and this pain blocking effect required no additional infiltration. Therefore, neosaxitoxin infiltration generates pain blockage that is locally maintained over a long period of time. Furthermore, with the dosage used no patient experienced adverse effects such as nausea or ataxia during or after treatment during the 3 months of clinical follow-up.

When conservative management of BPS fails, it has been recommended that prior to surgery patients begin pudendal nerve or sacral nerve neuromodulation therapies which have shown long-term success, or stimulation of the posterior tibial nerve, which tends to be less successful [21–23]. The use of botulinum toxin for BPS is considered only a fifth-line treatment prior to surgery, since it has shown variable effectiveness in different studies [24, 25]. Surgery is reserved as a last option in refractory cases. Patients with refractory BPS should be informed that surgery is the final option to try to relieve symptoms including pain, and that it may not be curative, even with cystectomy [26]. All of the treatments mentioned above come with high economic costs for the patient, both direct and indirect. Unfortunately, most patients in Chile cannot afford typical treatment, because their health insurance does not cover procedures for this condition [27]. In this context, neosaxitoxin infiltration could be a more economical, safe, and effective option for the general population.

BPS has a significant impact on the quality of life of patients by generating debilitating pain and urinary frequency and urgency that can lead to social isolation. For this reason, many women affected by BPS have associated psychiatric disorders, such as depression and anxiety [2]. Other medical conditions associated with BPS are inflammatory and painful chronic conditions such as fibromyalgia, vulvodynia, irritable bowel syndrome, and chronic fatigue syndrome [2, 28, 29]. In this study, after neosaxitoxin infiltration, all patients had remission of their psychiatric disorders associated with this pathology. Consequently, each woman had improved quality of life, which was evidenced by the reduction in the ICPI score. Moreover, with this treatment, all psychiatric and pharmacological costs were eliminated.

This pilot study included only five patients to explore the efficacy and safety of the use of neosaxitoxin as a long-acting pain blocker for BPS. To confirm these findings, the authors are currently performing a larger trial in the Hospital Clínico de la Universidad de Chile.

Conclusions

Neosaxitoxin infiltration was shown to be a safe and effective method for pain control in patients with BPS. Five patients diagnosed with BPS benefited from this innovative intervention. The efficacy of this therapeutic approach is higher than any other conventional treatment known to date, and the neosaxitoxin infiltration was well tolerated by the patients, with pain blockage and beneficial effects which lasted over the 90 days of follow-up after the initial infiltration procedure. As this is the first trial to test the effects of neosaxitoxin in the treatment of BPS, there are no previous findings with which to compare our finding that infiltration of neosaxitoxin leads to long-lasting pain relief and increased quality of life. The present findings demonstrate that neosaxitoxin is an innovative, new long-acting local pain blocker for BPS [13] with specific potential clinical use.

Conflicts of interest V. Manriquez and M. Naser received support from J&J to attend IUGA and ICS meetings. D. Castro, R. Guzmán, V. Iglesias, and N. Lagos report no conflicts of interest.

References

1. Hanno P, Lin A, Nordling J, Nyberg L et al (2010) Bladder Pain Syndrome Committee of the International Consultation on Incontinence. Neurourol Urodyn 29:191–198
2. 5th International Consultation on Incontinence (2012)
3. Rovner ES (2014) Interstitial cystitis. Medscape. http://emedicine.medscape.com/article/2055505-overview#a0156. Accessed 10 December 2014
4. Rosenberg MT, Hazzard M (2005) Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. J Urol 174(6):2231–2234

5. Offiah I, McMahon SB, O'Reilly BA (2013) Interstitial cystitis/bladder pain syndrome: diagnosis and management. Int Urogynecol J 24:1243–1256
6. Parsons C (2007) The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis. Urology 69(4):9–16
7. Brunstein R, Shapiro E, Kaye J et al (2008) The role of cystoscopy in the diagnosis of Hunner's ulcer disease. J Urol 180(4):1383–1386
8. Aihara K, Hiayama A, Tanaka N et al (2009) Hydrodistension under local anesthesia for patients with suspected painful bladder syndrome/interstitial cystitis: safety, diagnostic potential and therapeutic efficacy. Int J Urol 16(12):947–952
9. Lagos N (1998) Microalgal blooms: a global issue with negative impact in Chile. Biol Res 31(4):375–386
10. Lagos N (2014) Clinical applications of paralytic shellfish poisoning toxins. In: Rossini GP (ed) Toxins and biologically active compound from microalgae, vol 2. CRC Press, Taylor & Francis Group, New York, pp 309–329
11. Garrido R, Lagos N, Lattes K, Abedrapo M, Bocic G, Cuneo A et al (2005) Gonyautoxin: new treatment for healing acute and chronic anal fissures. Dis Colon Rectum 48(2):335–340
12. Rodriguez-Navarro AJ, Lagos N, Lagos M, Braghetto I, Csendes A, Hamilton J et al (2007) Neosaxitoxin as a local anesthetic: preliminary observations from a first human trial. Anesthesiology 106(2):339–345
13. Rodriguez-Navarro A, Lagos M, Figueroa C, García C, Recabal P, Silva P, Iglesias V, Lagos N (2009) Potentiation of local anesthetic activity of neosaxitoxin with bupivacaine or epinephrine: development of a long-acting pain blocker. Neurotox Res 16:408–415
14. Lattes K, Venegas P, Lagos N, Lagos M, Pedraza L, Rodriguez-Navarro AJ, García C (2009) Local infiltration of gonyautoxin is safe and effective in treatment of chronic tension-type headache. Neurol Res 31:208–233
15. Rodriguez-Navarro A, Berde CB, Wiedmaier G, Mercado A, García C, Iglesias V et al (2011) Comparison of neosaxitoxin versus bupivacaine via port infiltration for postoperative analgesia following laparoscopic cholecystectomy a randomized, double-blind trial. Reg Anesth Pain Med 36:103–109
16. O'Leary MP, Sant GR, Fowler FJ, Whitmore KE, Spolarich-Kroll J (1997) The interstitial cystitis symptom index and problem index. Urology 49:58–63
17. Lubeck DP, Whitmore K, Sant GR, Alvarez-Horine S, Lai C (2001) Psychometric validation of the O'Leary-Sant Interstitial Cystitis Symptom Index in a clinical trial of pentosan polysulfate sodium. Urology 57:62–66
18. Propert K, Mayer R, Wang Y et al (2006) Responsiveness of symptom scales for interstitial cystitis. Urology 67:55–59
19. Goin JE, Olaleye D, Peters KM, Steinert B, Habicht K, Wynant G (1998) Psychometric analysis of the University of Wisconsin Interstitial Cystitis Scale: implications for use in randomized clinical trials. J Urol 159:1085–1090
20. Colaco M, Evans R (2013) Current recommendations for bladder instillation therapy in the treatment of interstitial cystitis/bladder pain syndrome. Curr Urol Rep 14:442–447
21. Peters K, Feber K, Bennett R (2007) A prospective, singleblind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. BJU Int 100(4):835–839
22. Ghazwani Y, Elkelini M, Hassouna M (2011) Efficacy of sacral neuromodulation in treatment of bladder pain syndrome: long-term follow up. Neurourol Urodyn 30(7):1271–1275
23. Gajewski J, Al-Zahrani A (2011) The long-term efficacy of sacral neuromodulation in the management of intractable cases of bladder pain syndrome: 14 years of experience in one centre. BJU Int 107(8):1258–1264
24. Mangera A, Apostolidis A, Andersson KE, Dasgupta P, Giannantoni A et al (2014) An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. Eur Urol 65(5):981–990
25. Seth J, Khan M, Dasgupta P et al (2013) Botulinum toxin – what urologic uses does the data support? Curr Urol Rep 14:227–234
26. Rössberger J, Fall M, Jonsson O et al (2007) Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: sub-typing is imperative. Urology 70(4):638–642
27. Clemens J, Markossian T, Calhoun E (2009) Comparison of the economic impact of chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis/painful bladder syndrome. Urology 73(4):743–746
28. Clauw DJ, Schmidt M, Radulovic D et al (1997) The relationship between fibromyalgia and interstitial cystitis. J Psychiatr Res 31:125–131
29. Alagiri M, Chottiner S, Ratner V et al (1997) Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. Urology 49:52–57