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Urethral function in overactive bladder syndrome

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CHAPTER 6

INITIAL REPORT ON SUBTRIGONAL BOTULINUM TOXIN-A (BONT-A) THERAPY FOR FEMALE PATIENTS WITH URETHRAL INSTABILITY - RESULTS OF A PILOT STUDY

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INTRODUCTION

Overactive bladder syndrome (OAB) is a common, often under-diagnosed and under-treated condition that significantly affects the quality of life of patients[1].

Unfortunately, in large part of the patients the underlying etiology of OAB is unknown. Urodynamic evaluation can be performed to learn more of the underlying etiology, but unfortunately symptoms of OAB are also present in patients without urodynamic abnormalities. Therefore, patients with OAB are a very heterogeneous patient population for whom a standard treatment protocol is difficult to establish. The treatments offered to patients are usually by preference and experience of the treating physician and effectiveness is established by trial and error.

During filling cystometry of urodynamic evaluation for OAB, detrusor over activity (DO) is often observed. Urethral pressure variations – referred to as urethral instability (URI) by the International Continence Society (ICS)- have also been observed and associated with OAB[2,3]. However, the clinical relevance of this phenomenon is still controversial. DO can be observed in patients suffering from OAB, but also in asymptomatic patients. For urethral instability (URI), the presence of the phenomenon in asymptomatic volunteers was one of the major reasons to abandon this as a pathophysiological phenomenon. It never made it to stay within the International Continence Society (ICS) terminology.

Urinary continence is maintained by a low pressure reservoir and adequate resting pressure in the urinary sphincter. Therefore, the scope of research on OAB should not be limited to (over)activity of detrusor muscle, but should also take urethral function in consideration. This opinion is shared by the International Consultation on Incontinence Research Society (ICIRS), who recommended new clinical research to be performed on urethral pressure variations[4]. In a recent review was concluded that despite the poor methodological quality of the performed studies UPV may be regarded a –potentially pathophysiological- entity of its own within cohorts of patients with OAB[5]

Nowadays treatment options for OAB include lifestyle modifications, pelvic floor muscle exercises, pharmacotherapy with anticholinergics or beta-3 receptor agonists, pudendal or sacral nerve stimulation and intravesical Botulinum toxin-A (BoNT-A) therapy[6]. In the past, surgical bladder denervation has been performed as treatment modality for OAB.

This was first described in 1935 by Richer and afterwards modified by several colleagues[7,8].

All the above mentioned treatments have in common that they interfere in any part of efferent and afferent signaling from the bladder to the brain, the difference is in the localization and extent of interference. In the present day invasive surgical denervation is rarely performed. The signaling from the nerves is blocked by intravesical injections of Botulinum toxin A, it is a chemical denervation. Botulinum toxin A treatment in OAB has evidence based good results[9], however there are still patients suffering from refractory OAB. The former surgical denervation was performed outside the bladder wall, and thus had a different location of action than the current chemical intravesical injections.

We hypothesized that patients with OAB symptoms and URI are more likely to benefit from a treatment with the mode of action at the urodynamically identified problem.

In this pilot study we present the clinical and urodynamic results of subtrigonal / paraurethral chemical denervation treatment with BoNT-A injections in 5 patients with refractory OAB symptoms and URI.

MATERIAL AND METHODS

This is a retrospective description of the pilot study we performed in 5 female patients. All patients were referred to the Urology department of Leiden University Medical Center and received already several treatments for OAB without success. Four patients had a long history of refractory idiopathic OAB symptoms. One patient was diagnosed with Bladder Pain Syndrome (BPS). All patients were evaluated by an urodynamic study with urethral pressure measurement. All urodynamic studies demonstrated urethral pressure variations.

In the past, improvement of OAB after subtrigonal injections with local anesthetics were a positive predictive factor for success of surgical denervation⁷. Prior to the surgical procedure, local instillation with xylocaine / adrenalin or bupivacain solution was performed. First unilaterally, subtrigonal, into the anterior fornix lateral, one cm to the cervix and at a depth of about 3 cm. When there was an improvement of compliance or DO on cystometry and post void residual volume was less than 150ml, there was a favorable result and treatment was continued with surgery. Resection of nerves was performed unilaterally or bilaterally

through an incision in the anterior vaginal wall. Therefore we started treatment with subtrigonal / paraurethral injections of 10cc lidocaine 1%. The patient was positioned in dorsolithotomy position. After disinfection, a urinary catheter was introduced. Traction on the balloon of the catheter was used to localize the position of the bladder neck and the trigonum. Here, 10mL of lidocaine was injected using a 22 gauge spinal needle. The patients were contacted the following day by telephone to evaluate the efficacy of the injections. An improvement of 50% or more in the complaints of urgency and/ or urge urinary incontinence was considered as a positive response. If the response was positive, treatment was continued with subtrigonal injections BoNT-A, 100IU in 10ml solution of NaCl 0,9%. A description of the patients is mentioned below.

Patient 1

Female nulliparous patient of 57 years old referred with urge urinary incontinence. History of slow transit constipation and bowel outlet obstruction, abdominal uterus extirpation and PDDNOS. Patient was referred with refractory OAB with urinary incontinence. She had pelvic floor muscle therapy (PFMT) and anti-muscarinic therapy without effect. Physical examination demonstrated no pelvic organ prolapse (POP). Cystoscopy revealed no abnormalities. Urodynamic evaluation demonstrated bladder capacity (BC) of 380ml, no detrusor overactivity (DO), normal compliance, high urethral pressures till 100 cmH₂O and urethral pressure variations (UPV). After repeated PFMT without success, treatment with alpha blocking agent was started, without success. She was treated with subtrigonal lidocaine injections, which improved her symptoms with more than 50%. Treatment was continued with subtrigonal BoNTA injections.

Patient 2

Female nulliparous patient of 38 years old. History of fibromyalgia. Patient was referred with OAB. She already received anti-muscarinic treatment, PMFT and intravesical glycosaminoglycanes (GAG)-replacement therapy with our success. Physical examination demonstrated no POP. Urinary test were clear. Cystoscopy revealed no intravesical abnormalities. Urethra was dilated with short relieve of symptoms (2 days). Bladder diary mentioned total volume 1120ml. Urinary portions of 60-250ml. Daytime frequency

of 7 times, 1 time nocturia. Urodynamic evaluation demonstrated BC of 329 ml, no DO. First sensation of filling (FSF) at 64ml with urethral pressure drop. High urethral pressures and UPV of > 40 cm H₂O. She had a very good response after subtrigonal lidocaine injections, so treatment was continued with subtrigonal BoNT-A-injections.

Patient 3

Female patient of 69 years old referred with urge urinary incontinence. History of Stamey procedure, TVT-O and later TVT. Physical examination demonstrated no POP. Patient reported daytime frequency of 8 times and at night 1 time, volumes 75-200ml. Three to four incontinence episodes per day. Cystoscopy demonstrated trabeculation. Urodynamic evaluation demonstrated BC of 407ml, no DO, FSF at 199ml with high pressure drops of urethral pressure and observation of urinary incontinence occurring at lowest pressure point. After successful treatment with lidocaine injections, treatment was continued with subtrigonal BoNT-A injections.

Patient 4

Female multiparous patient of 62 years old referred with mixed urinary incontinence. No relevant medical history. Physical examination demonstrated POP. Urinary test were clear. Bladder diary demonstrated daytime frequency of 12 times and at nighttime frequency of 3 times. Nine tot ten incontinence episodes per day. Cystoscopy demonstrated trabeculation. Urodynamic evaluation demonstrated BC of 337ml, no DO, FSF at 116ml. High urethral pressures up to 180 cmH₂O UPV of > 40 cm H₂O. Post void residual volume was 225ml. She had a good response after subtrigonal lidocaine injections, so treatment was continued with subtrigonal BoNT-A-injections.

Patient 5

Female patient of 62 years old referred with urethral- and bladder pain syndrome. History of fibromyalgia, chronic fatigue syndrome, cardiac arrhythmias and nocturnal enuresis in her childhood. Patient suffered from urethral pain since 2010, she was treated with alpha blocking agents, anti-muscarinic therapy without any effect and local depomedrol application with partial response. Physical examination demonstrated no

POP or other abnormalities. Urinary tests were normal. Her bladder diary showed daytime urinary frequency of 11 times with volumes of 300-450ml. Nocturia 2-3 times. Cystoscopy revealed trabeculation. Urodynamic evaluation demonstrated BC of 730ml, no DO, normal compliance, FSF at 113ml, high urethral pressures up to 150 cmH₂O and UPV of > 40 cm H₂O. There was no post void residual volume. The pain worsened after micturition. She had a positive response after subtrigonal lidocaine injections, so treatment was continued with subtrigonal BoNT-A-injections

RESULTS

The urodynamic evaluations before and after the subtrigonal BoNT-A injections and the clinical efficacy were compared. In table 1, results of pre- and post-treatment urodynamic results are summarized.

Patient 1

There was a good response to BoNT-A injections for four months. Urodynamic evaluation after the second series of injections demonstrated BC of 480 ml, no DO, still there was high urethral pressure around 100 cmH₂O, but no pressure variations were demonstrated. Treatment has been successfully repeated.

Patient 2

Urge complaints responded good on this treatment. Urodynamic evaluation after treatment demonstrated BC of 363 ml, no DO, FSF of 200ml and 114ml. UPV were still present, but with variations of maximal 20 cmH₂O. Subtrigonal BoNT-A treatment has been repeated several times, with good response.

Patient 3

Patient had a good response after subtrigonal BoNT-A-injections. Urodynamic evaluation after BoNT-A treatment demonstrated BC of 687 and 756ml, no DO, FSF at 613 and 645ml. UPV were observed, but with maximal pressure drops of 20cm H₂O and not related to FSF.

Patient 4

Patient had a good response after subtrigonal BoNT-A-injections. Because of hip replacement surgery, post-treatment urodynamic evaluation has not been performed yet.

Patient 5

Patient had no positive response. After a few days she developed a urinary tract infection. After treating this infection, her complaints were as worse as before treatment.

DISCUSSION

In this heterogeneous group of patients with urethral instability (URI), we demonstrated an improvement of complaints in four out of five patients treated with subtrigonal BoNT-A injections. An interesting finding, apart from the increased bladder capacity, is the increased bladder volume at FSF.

Groenendijk et al concluded that presence of URI was a positive predictive factor for success of sacral neuromodulation therapy (SNM) for OAB[10] and a better predictive factor than presence of DO in pretreatment urodynamic evaluation. Patients with URI responded well on SNM, however, URI was still present in post treatment urodynamic evaluation. Consistent with these findings, in our study, UPV were still present in post-treatment urodynamic evaluation, but with a decreased amplitude of the variations. Sixty years ago, in the time of Ingelman-Sundberg, a group of 34 patients treated with surgical denervation was already split into 6 different categories, indicating how heterogeneous the patient population with OAB is and has been over the years. Thirty patients were cured of their symptoms, with mean follow up of seven years[7]. At that time, changes in cystometry and in compliance of the bladder were observed. Urethral pressures were not measured in those days.

Classification based on clinical and urodynamic characteristics of OAB patients would contribute to targeted therapy. To debate is the question whether OAB is from urodynamic point of view a bladder-only problem or not. In the recent decades, urodynamic evaluation of patients have been further developed. An effort has been made to define what

observations are normal or physiological and when to speak of abnormal or pathophysiological findings. However, the bladder has been the center of attention. If assumed that the feeling of imminent micturition has its origins in the urethra[11], intervening in afferent sensory input from the urethra could have a positive effect on OAB symptoms of patients. It might be that efferent motor response is being of lesser importance. Apparently, sensory input is influenced by neuromodulation and surgical or chemical denervation.

Local injections with lidocaine temporarily and reversibly prevent the formation and transmission of stimuli along the peripheral nervous pathways and nerve endings, creating a temporary numbness. BoNT-A results in inhibition of exocytosis of acetylcholine containing vesicles at the motor endplate, making transmission of the nerve impulse to the motor endplate of the muscle impossible and resulting in a weak paralysis. Despite the differences in mechanism of action of BoNT-A and lidocaine, local injections with lidocaine have been of predictive value in regard to response on BoNT-A treatment[7,8].

Probably, we should see OAB as a form of neuropathy or bladder nerve supply dysfunction that has different forms of expression. Depending on the affected branches, different complaints will be reported as major complaint of the patients, resulting in a heterogenous population with multiple complaints within pudendal nerve supply area.

CONCLUSIONS

Chemical denervation by subtrigonal BoNT-A injections resulted in improvement of refractory OAB symptoms in four out of five patients. The largest improvement was in FSF. Further prospective research is necessary to define the condition of URI in patient with OAB. Besides, new treatment modalities like chemical denervation with subtrigonal BoNT-A injections should be explored by correlation of bladder diaries, validated questionnaires and urodynamic evaluations, with special attention for FSF.

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