

BOTULINUM TOXIN IN THE TREATMENT OF CYSTITIS

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Abstract

Objective. This study will follow the effectiveness of treatment of chronic cystitis in menopausal women, associated with overactive bladder syndrome, performed by endoscopic injection of botulinum toxin type A to patients who previously attended drug treatment and bladder instillation treatment but with persistence of clinical manifestations.

Materials and methods. We studied 43 patients, in menopause with chronic recurrent cystitis and overactive bladder. The data were statistically analyzed by descriptive analysis and linear regression. We used Chi-square, T-Student test. Treatment was performed by injecting botulinum toxin solution.

Results. The patients were divided in 2 groups. Group A, 22 patients underwent instillation treatment. Group B, 21 patients, underwent endovesical injection of botulinum toxin type A. 18 patients in group A after treatment showed an initial improvement of symptoms; after 3 months evaluation the improvement was in 63.63% and after 6 months only 54.54%. The B group after 2 weeks of treatment 85.71% had remission of symptoms.

Conclusions. Endoscopic treatment by injection of type A botulinum toxin in bladder mucosa represents a feasible therapeutic approach.

Keywords: overactive bladder syndrome, endovesical injection of botulinum toxin type A, chronic cystitis.

TRATAMENTUL CISTITEI CRONICE CU TOXINA BOTULINICĂ

Rezumat

Obiective. Studiul urmărește eficacitatea tratamentului cistitei cronice asociată cu sindromul vezicii hiperactive la femeile aflate la menopauză, cu toxina botulinică de tip A administrată prin injectare endoscopică, la paciente la care a existat persistența manifestărilor clinice după tratament medicamentos și instilații vezicale.

Material și metode. Au fost luate în calcul 43 de paciente aflate la menopauză, diagnosticate cu cistită cronică recurentă asociată cu vezică hiperactivă. Datele obținute au fost analizate statistic prin analiză descriptivă și regresie liniară. S-a folosit testul Chi-square și testul T-student. Tratamentul a fost realizat prin injectare de soluție cu toxină botulinică.

Rezultate. Pacientele au fost împărțite în două grupuri. Grupul A, format din 22 de paciente, a urmat un tratament prin instilații vezicale. Grupul B, format din 21 de paciente, a urmat un tratament prin injectare endoscopică de toxină botulinică de tip A. După administrarea tratamentului, 18 paciente din grupul A au prezentat o îmbunătățire în ceea ce privește simptomele; după 3 luni de evaluare îmbunătățirea a fost resimțită de 63,63% dintre paciente, iar după 6 luni aceasta a ajuns la 54,54%. În grupul B, după 2 luni de tratament, 85,71% dintre paciente au resimțit îmbunătățiri în ceea ce privește simptomele.

Concluzie. Tratamentul prin injectare endoscopică de toxină botulinică în mucoasa vezicii urinare reprezintă o alternativă terapeutică demnă de luat în seamă.

Cuvinte cheie: sindromul vezicii neurogene (hiperactive), injectare endovezicală de toxină botulinică de tip A, cistită cronică.

INTRODUCTION

Painful bladder syndrome overactive bladder, interstitial cystitis, are characterized by urgency with or without incontinence, usually associated with high urinary frequency and nocturia in the absence of infection. This affects all major aspects of quality of life: social, psychological, occupational, domestic, physical and sexual. Most cases of uncomplicated cystitis occur in women; each year approximately 10% of women recounts an episode of UTI annually and over 50% of the female population has at least one such infectious episode during their lifetime. Simple cystitis occasionally occurs in prepubertal girls; the incidence is increased in late adolescence and during two three decades of life.

MATERIALS AND METHODS

This study will follow short and medium-term evaluation of the effectiveness of treatment of chronic cystitis in menopausal women, associated with overactive bladder syndrome, performed by endoscopic injection of botulinum toxin type A to patients who previously attended drug treatment (antibiotic, inflammatory) and bladder instillational treatment but with persistence of clinical manifestations. The study was conducted on a total of 43 patients, aged between 42 and 65 in menopause, with chronic recurrent cystitis and overactive bladder in the period January 2004 - June 2008, in the Clinical Institute of Urology and Renal Transplant of Cluj Napoca and Gynecology I Clinic of Cluj Napoca after obtaining written informed consent of subjects to participate in the study. Patients who had undergone all stages of evaluation, a questionnaire assessment of symptoms, clinical examination, uroculture, ultrasound, uroflow-meters and cystoscopy to rule out other associated pathologies, the need was made urography and / or CT were introduced in the study. Follow up for the patients was performed at 2 weeks, 1 month, every 3 months to 1 year and consisted of a clinical examination, ultrasound evaluation questionnaire of symptoms and endoscopic reassessment after treatment.

The data collected were statistically analyzed by descriptive analysis and linear regression. The descriptive analysis highlighted differences between the groups. The main statistical methods used, were percentage expression, mean values with standard deviation.

Null hypothesis is used to define the significance of the difference. A statistical null hypothesis that denies the similarity between the two groups was used, the difference being a consequence of the therapeutic study. Correlation analysis was done by Chi-square calculation for qualitative values expressed as a percentage and T-Student test for quantitative values expressed as mean values with standard deviation. Simple linear regression using mean square

error calculation was also used. We used the Epi-Info 3.5.3 statistical program from the Center for Control and Prevention USA disease.

In initial empirical antibiotic therapy fluoroquinolones provides an excellent spectrum in most cases and the duration of administration is 7 days. When bacterial susceptibility data are available modifications are made. Associated antibiotic treatment with NSAIDs, preferably administered orally or rectal suppository form can remove or diminish some symptoms and signs of inflammation.

Together with drug treatment, intravesical instillation is carried out for 10 days using a silver nitrate solution associated with Heparin 25,000 IU %_o alternating with dexamethasone 8 mg / 2 ml with 4.2% sodium bicarbonate. To view and evaluate the lower urinary tract lesions cystoscopy was used.

The method of treatment is performed by injecting botulinum toxin solution in 20 to 30 points covering the entire surface of detrusor, avoiding the bladder trigone area and 1 cm around the ureteric orifices. The bladder is filled with 100 ml saline. The injection solution is prepared as follows: 100 IU Botulinum toxin is diluted in 8ml 9% saline, then 4 of the 8 ml are withdrawn into a syringe of 20 ml and diluted with another 11 ml of saline resulting in a total of 15 ml; the same is done with the other 4 ml.

RESULTS

The 43 patients included were divided according to the treatment followed in 2 groups. Group A, 22 patients underwent instillational treatment and those in group B with 21 patients, underwent endovesical injection of botulinum toxin type A. All patients had negative urinalysis before they had submucous injection of botulinum toxin type A. A total of 8 patients who underwent endoscopic treatment with submucous injection of botulinum toxin, had vesico-ureteral reflux which was previously treated. Atrophic mucosa was found at postmenopausal patients which imposed hormonal therapy with estrogen. We used questionnaires to quantify and evaluate the quality of life score (Table I, Table II).

Table I. Quality of life evaluation.

Symptom score		Quality of life score	
At urgency is it difficult to hold in your urine?	0	How much does this affect you?	0
	1		1
	2		2
	3		3
Do you have a problem with going to the bathroom often during the day?	0	How much does this affect you?	0
	1		1
	2		2
	3		3
Do you wake up during the night to go to bathroom?	0	How much does this affect you?	0
	1		1
	2		2
	3		3
Do you have urine leaks?	0	How much does this affect you?	0
	1		1
	2		2
	3		3
Total		Total	

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Table II. Interpretation.

Symptom score	Interpretation	Quality of life score	Interpretation
0	No urinary symptoms	0	You are not affected by urinary symptoms
1-3	Your symptoms are light	1-3	You are a little bothered by your symptoms
4-6	Your symptoms are moderate	4-6	You are moderately bothered by your symptoms
7-9	Your symptoms are severe enough	7-9	Your symptoms are quite annoying
10-12	You have very serious problems	10-12	Your symptoms are a major problem

Patients in group A after treatment showed an initial improvement of symptoms (Figure 1). At 3 months evaluation the favorable results were 63.63 %. At 6 months evaluation the number of patients with favorable results was reduced; thus only 54.54% had significant remissions of symptoms. Patients from group B after 2 weeks of treatment 85.71% had remission of symptoms. As a side effect we found incomplete urine retention evidenced by ultrasound measurement of post-micturition residues which under treatment disappeared at 1 month. One patient required re-injection of botulinum toxin because of persistent clinical signs.

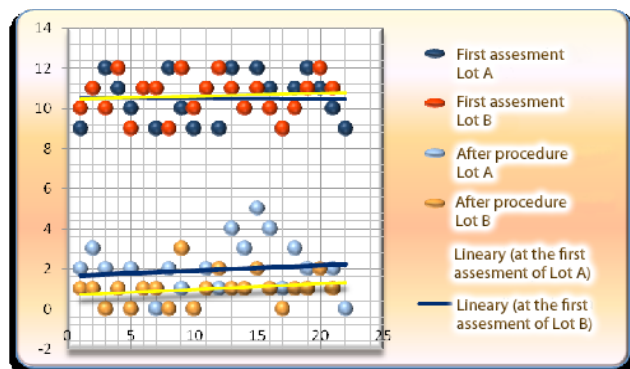


Figure 1. The initial assessment symptom score compared with review conducted at 1 month after treatment.

Linear projection of symptom score marks clearly the difference between the two groups at 12 months (Figure 2). The quality of life score had a similar development of symptoms and the recurrence of clinical symptoms is reflected in the quality of life of these patients. Linear representation of the quality of life score of patients in group B shows, while maintaining the favorable effect of treatment, the difference is minimal between the two assessments. From the initial assessment it can be considered that these patients are cured. But the patients from group A show a deterioration in the quality of life with a recurrence of symptoms.

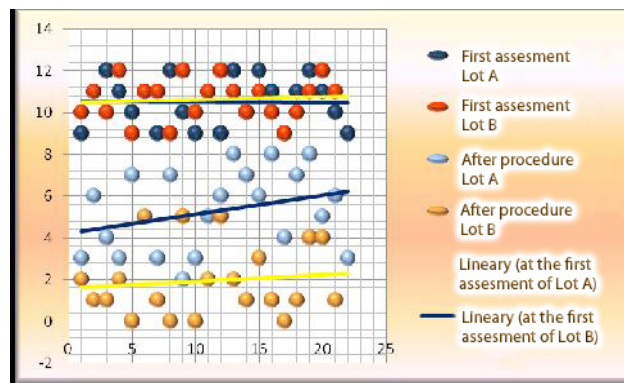


Figure 2. The initial assessment symptom score compared with reassessment at 12 months after treatment

An objective method to diagnose overactive bladder represented by the uroflow-metry brings data that can be quantified and compared. We can make a differential diagnosis with pathology (eg Bladder outlet obstruction. In the case of an overactive bladder maximum bladder capacity is much reduced from normal. Under various treatments this can be improved even to reach normal levels The average volume at patients with an overactive bladder from study was 267 ml (\pm DevSt 3). At 6 months following treatment the average volume showed a rise both for patients in group A but significantly from those in group B.

Bladder detrusor hyperreactivity and uninhibited bladder contractions may be recorded by uroflow-meters during bladder filling phase. Uroflow-metry is an objective method for assessing overactive bladder syndrome. If the female bladder normally has a capacity of up to 500-600 ml, for patients with overactive bladder the average was only 267 ml (\pm DevSt 3) (Figure 3). Uninhibited bladder contractions corresponding to OAB manifestations appear suddenly at an increased pressure in the bladder, so the initial assessment mean detrusor pressure was 63.4 m H₂O registration (\pm DevSt \pm 2) (Figure 4).

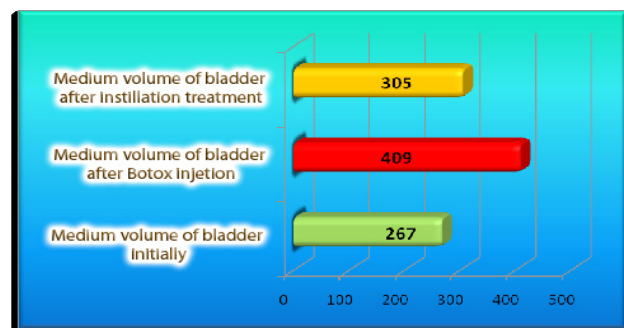


Figure 3. Average bladder volume uroflow-metric measured at baseline and at 6 months after treatment.

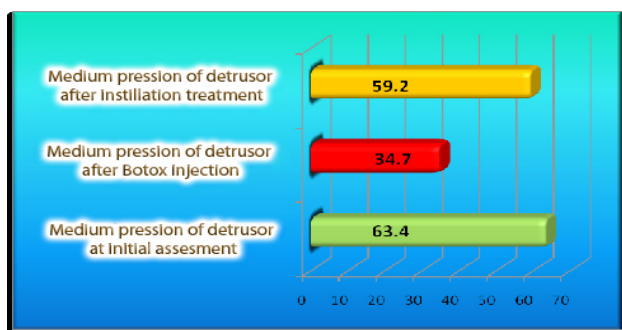


Figure 4. The average pressure of the bladder detrusor uroflow-metric measured at baseline and at 6 months after treatment.

If the initial average detrusor pressure recorded high values, these are significantly improved after treatment of intravesical Botox injection. The average value measured at the first evaluation was 63.4 cm H₂O (DevSt \pm 2), for patients in group B it decreased to 34.7 cm H₂O (DevSt \pm 1) (an improvement of 45.26%) ($p=0.0059$). A slight improvement is recorded for patients in group A (6.62%) ($p=0.0834$) (Figure 4).

DISCUSSION

Chronic cystitis requires particular attention because it has the potential to develop into aggressive forms of solution which can sometimes only be solved through major surgery. The treatment is often not easy and in most times the etiopathogenetic and maintenance mechanism are overlapping and the therapy can only temporary improve the development. Overactive bladder syndrome may be associated and confused with manifestations of chronic cystitis, but without an effective treatment can persist or get worse. Regarding therapy, the physician should provide the most effective method of treatment with the less side effects but with good long/medium-term success, without engaging the patient in expensive therapies with doubtful outcomes.

CONCLUSIONS

Endoscopic treatment by injection of type A botulinum toxin in bladder mucosa represents a feasible therapeutic approach.

Improvement or disappearance of clinical manifestations associated with chronic cystitis and with overactive bladder in women at menopause are installed immediately post procedural and maintained throughout the follow-up.

Treatment of associated pathology (vesico-ureteral reflux, endocrine disorders) need to be performed before endoscopic injection botulinum toxin type A to obtain effective and lasting results.

Overactive bladder syndrome requires a correct diagnosis and appropriate treatment to exhibit persistent results.

Overactive bladder syndrome untreated or undiagnosed can properly engage, in economic terms, high costs for both the health system and for the patients.

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