

ORIGINAL ARTICLE

Intravesical instillation of onabotulinum toxin A embedded in inert hydrogel in the treatment of idiopathic overactive bladder: A double-blind randomized pilot study

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ABSTRACT

Objective. It was hypothesized that increasing the time for which onabotulinum toxin A (OnabotA) is exposed to the urothelium following intravesical instillation will augment its effect. TC-3 is an inert heat-sensitive hydrogel, which creates an intravesical bulk providing a slow release of the embedded drug after instillation. The aim of this study was to evaluate the effect of OnabotA, embedded in inert TC-3 hydrogel, in patients with idiopathic overactive bladder (OAB).

Methods. In total, 39 female patients (age 30–65, average 53.8 years) with OAB symptoms were randomized for the study into four groups, each receiving 50 ml of the following intravesical instillations: Group A, 0.9% NaCl (placebo, $n = 11$); Group B, TC-3 gel + 200 U OnabotA ($n = 9$); Group C, TC-3 gel + 200 U OnabotA + dimethyl sulfoxide (DMSO) ($n = 10$); and Group D, DMSO ($n = 9$). The parameters were compared before and 1 month after treatment.

Results. When comparing parameters using conventional statistical methods (Kruskal–Wallis test), no statistically significant changes were observed within the groups. Comparison of the medians using an analysis based on the mathematical gnostics showed the superiority of the method used in Group B over the other groups in the following parameters: number of urgency grade 3 + 4 episodes/72 h, number of leakage episodes/72 h, Overactive Bladder Questionnaire total score and Patient Perception of Bladder Condition total score. Group D showed its superiority over the other groups in respect to the number of nocturia episodes/72 h.

Conclusions. The results indicate that intravesical instillation of OnabotA, embedded in TC-3 gel, could become an alternative to intramural injection for a well-selected subgroup of patients.

ARTICLE HISTORY

Received 22 June 2015
Revised 26 October 2015
Accepted 13 November 2015

KEYWORDS

Intravesical instillation; onabotulinum A; overactive bladder; TC-3 hydrogel; urothelium

Introduction

Overactive bladder (OAB) syndrome is defined by the International Continence Society as urgency with or without urge urinary incontinence, usually accompanied by increased daytime frequency and nocturia, in the absence of urinary tract infection (UTI) or other obvious pathology [1,2]. Behavioural therapy (i.e. fluid intake regulation, weight loss, caffeine reduction, bladder retraining) is the first line of treatment. Pharmacotherapy using anticholinergics or betamimetics remains the most widely used treatment option for OAB.

For those who do not respond to oral drug therapy, more invasive interventions are available. Those include onabotulinum toxin A (OnabotA) injections into the bladder wall and peripheral or sacral neuromodulation. Surgery may be carried out as a last resort.

OnabotA is considered an excellent therapeutic option for bladder overactivity [3]. The intramural OnabotA injection, currently the only established means of administration, is invasive, often requiring intravenous sedation or anaesthesia. The consequences of repeated injections are not yet fully

known [4]. It is clear that, if it could be shown to be effective, a less invasive mode of delivery of OnabotA would be preferable.

Several studies have tested the functional consequences of intravesical instillation of OnabotA in animal models. Based on these studies, it was proposed that OnabotA exerts its effect through afferent rather than efferent mechanisms. With the urothelium and lamina propria being the key components of bladder sensory signalling, OnabotA instillation could potentially provide relief of OAB symptoms [5].

Only a few open-label studies have tested the efficacy of OnabotA instillation in patients with OAB. In a previous pilot clinical trial by this group, a significant decrease was observed in the frequency of urge incontinence episodes, as well as an increase in the volume during the first involuntary detrusor contraction. However, unlike intramural OnabotA injection, no effect on detrusor contractility was observed following intravesical instillation. The mean duration of clinical improvement was 6.8 weeks [6]. Since then, others have attempted to administer OnabotA intravesically while facilitating the process of crossing the urothelium using pretreatment with dimethyl

Table 1. Subjects' baseline characteristics.

Variables	Group A	Group B	Group C	Group D	p
Demographics					
Age (years)	52.2 ± 9.1	52.3 ± 8.4	55.3 ± 11.9	55.6 ± 7.0	0.7720
Weight (kg)	77.3 ± 11.4	81.8 ± 13.9	91.5 ± 19.8	74.3 ± 11.5	0.0683
Body mass index (kg/m ²)	28.4 ± 4.8	30.5 ± 5.9	33.4 ± 8.1	27.9 ± 4.6	0.1837
Uroflowmetry					
Voided volume (ml)	250.9 ± 112.2	313.0 ± 126.7	238.5 ± 114.0	247.8 ± 76.8	0.2698
Maximal flow rate, Q_{max} (ml)	24.9 ± 10.2	28.0 ± 7.6	20.2 ± 9.1	22.8 ± 7.9	0.2825
Postvoid residual (ml)	1.8 ± 0.0	6.5 ± 0.0	6.0 ± 0.0	11.1 ± 0.0	0.1056
Pressure/flow study					
Cystometric capacity (ml)	243.9 ± 106.9	279.4 ± 118.0	261.2 ± 80.0	207.4 ± 75.4	0.4462
Compliance (ml/1 cmH ₂ O)	46.5 ± 27.8	53.1 ± 32.3	47.8 ± 19.6	70.6 ± 71.1	0.9620
Maximal detrusor pressure during voiding, p_{det} (cmH ₂ O)	31.0 ± 17.5	35.6 ± 13.3	27.0 ± 17.2	35.0 ± 19.6	0.6934
Bladder contractility index	112.5 ± 47.0	113.0 ± 50.1	118.0 ± 25.1	100.3 ± 33.6	0.8368
Three day voiding diary					
No. of micturitions/72 h	36.4 ± 10.0	34.7 ± 10.1	34.7 ± 7.4	33.4 ± 8.0	0.9093
Average voided volume (ml)	166.5 ± 51.2	209.7 ± 44.6	149.8 ± 60.4	150.9 ± 30.4	0.4170
No. of urgency grade 3 episodes/72 h	11.7 ± 8.3	16.8 ± 9.6	8.5 ± 3.4	12.1 ± 3.9	0.0934
No. of urgency grade 4 episodes/72 h	5.4 ± 6.9	6.0 ± 3.6	1.3 ± 1.9	1.8 ± 2.9	0.0419
No. of leakage episodes/72 h	5.5 ± 7.4	4.8 ± 4.3	2.4 ± 2.3	2.3 ± 3.0	0.5310
No. of nocturia episodes/72 h	2.8 ± 2.6	3.0 ± 2.6	3.7 ± 3.9	3.8 ± 3.6	0.9377
OAB-q					
Total score	101.7 ± 30.4	104.0 ± 35.7	84.0 ± 28.3	103.3 ± 32.4	0.4527
PPBC					
Total score	4.4 ± 0.7	4.9 ± 0.9	4.3 ± 0.8	4.7 ± 0.9	0.3744

OAB-q = Overactive Bladder Questionnaire; PPBC = Patient Perception of Bladder Condition.

sulfoxide (DMSO), attaching the large OnabotA molecule to liposomes or using electromotive drug administration [7,8].

This current pilot study was designed to test the hypothesis that increasing the duration of OnabotA exposure to the urothelium may augment its effect to the level of clinical significance. OnabotA was mixed with the inert biocompatible TC-3 gel. TC-3 is a heat-sensitive hydrogel, which is liquid at 5 °C and solidifies at body temperature. After intravesical instillation, the TC-3 gel creates an intravesical bulk, providing a slow release of the embedded drug.

The aim of this study was to evaluate whether combining OnabotA with TC-3 would improve its treatment effects in idiopathic OAB patients.

Methods

Patients

In total, 43 female patients (age 30–65, average 53.8 years) with OAB symptoms were screened and 39 of them were randomized for the study. Of those, 37 (37/39; 94.9%) had been treated previously with anticholinergics and 29 (29/37; 78.4%) of these patients considered this treatment to be effective.

Subjects with the following conditions were excluded from participation in the study: individuals over the age of 65 years, and those with symptomatic UTI, significant stress or mixed urinary incontinence where stress was the predominant factor, those using intermittent catheterization or those with an indwelling catheter, a postvoid residual (PVR) of more than 200 ml, a clinically significant pelvic organ prolapse, diabetic neuropathy, neurogenic bladder, clinically significant bladder outlet obstruction, a history of previous malignant disease in the pelvic area, previous irradiation to the pelvis or a positive pregnancy test.

All subjects were informed about the risks associated with the study and provided written, informed consent. The study protocol was approved by the ethics committee of the University Hospital, Ostrava. The study was designed in accordance with the principles of the Declaration of Helsinki, World Medical Association. The EudraCT number of this study is 2012-005344-15. Subjects' baseline characteristics are summarized in Table 1.

Study design

After signing the informed consent, all patients were asked to discontinue anticholinergic medication. After a 2–3 week washout period, baseline assessment was performed. The Overactive Bladder Questionnaire (OAB-q) and Patient Perception of Bladder Condition (PPBC) scale were used for subjective self-assessment. All questionnaires and scales used in this study were validated in the subjects' native language. A 3 day voiding diary was maintained to assess the frequency of micturition and the number and severity of the urgency episodes. Uroflowmetry and pressure/flow studies were used to obtain the objective data. The invasive urodynamic evaluation (MMS, Enschede, the Netherlands) was performed using a 6Ch bladder catheter in the sitting position, with the filling rate determined as one-tenth of the average functional bladder capacity reported in the voiding diary (e.g. 300 ml capacity = 30 ml/min filling rate). A catheter was inserted into the rectal ampulla to measure the intra-abdominal pressure. Both catheters were zeroed against atmospheric pressure at the level of the symphysis according to good urodynamic practices [9].

All assessments were performed immediately before and 1 month after the treatment.

Table 2. The instillation scheme.

Group	Group description	1st instillation (30 min)	2nd instillation (as long as possible)
Group A: Placebo	Saline	50 ml 0.9% NaCl	50 ml 0.9% NaCl
Group B: Active treatment	BoNT-A in TC-3 gel	50 ml 0.9% NaCl	200 U BoNT-A in 50 ml TC-3 gel
Group C: Active treatment	DMSO plus BoNT-A in TC-3 gel	50 ml 25% DMSO	200 U BoNT-A in 50 ml TC-3 gel
Group D: Active treatment	DMSO	50 ml 25% DMSO	50 ml 0.9% NaCl

BoNT-A = botulinum neurotoxin type A; DMSO = dimethyl sulfoxide.

Randomization and blinding

The following agents were used in this prospective randomized double-blind study: 0.9% NaCl as the placebo, OnabotA (Botox®; Allergan, Westport, Ireland) and DMSO 25% (Rimso; Bionicle Pharma, Toronto, Canada).

Patients enrolled into the study were randomized into four groups, each receiving 50 ml of the following intravesical instillations: Group A, 0.9% NaCl (placebo treatment, $n = 11$); Group B, TC-3 gel (TheraCoat, Raanana, Israel) + 200 U OnabotA ($n = 9$); Group C, TC-3 gel + 200 U OnabotA + DMSO ($n = 10$); and Group D, DMSO ($n = 9$).

Patients' eyes were covered during the procedure to blind them to the treatment. The 0.9% saline and 25% DMSO were stored in the fridge so that their temperature during instillation would be the same as the TC-3 gel. As DMSO requires instillation 30 min before the instillation of the TC-3 gel and OnabotA, all instillations were performed in a biphasic manner (to keep the patient blinded to the treatment). The members of the study team performing the randomization and instillation were unblinded but they had no access to the patient data obtained during the clinical visits and did not participate in the data analysis. Investigators involved in the processing and analysis of the data were blinded to the nature of the treatment.

Procedure

OnabotA was reconstituted in 2 ml of 0.9% saline and then mixed with 48 ml of TC-3 gel immediately before instillation. With the patient in the lithotomy position, the urethral orifice was cleaned in the standard fashion, and a single-use sterile catheter (18 Ch) was inserted into the bladder. After draining the bladder, 50 ml of saline or DMSO was instilled and kept in place for 30 min, then the bladder was emptied again. This was followed by instillation of 0.9% saline or OnabotA mixed with TC-3 gel. The catheter was then removed and the patients were advised to delay micturition as long as possible. The elapsed time until the first micturition was recorded.

The instillation scheme is summarized in Table 2.

Statistical analysis

Data were processed and statistical analyses performed by the Number Cruncher Statistical System (NCSS). Data are expressed as mean \pm standard deviation. Changes in time and differences between groups were assessed using the non-parametric Kruskal–Wallis one-way analysis of variance (ANOVA) test. A p value ≤ 0.05 was considered statistically significant.

Mathematical statistical analysis was not the best tool for analysis of the data because (i) the sample size was between 9

and 11 in each group; (ii) there was high inherent inter-individual and intraindividual variability; (iii) the data probability distributions were non parametric; (iv) they were highly heterogeneous; and (v) the outliers contained very valuable information that would have been missed if the standard statistical tests had been applied. Therefore, non-statistical methods based on mathematical gnostics were used. The method incorporates robust probability distribution of different parameters at multiple time-points with an emphasis on the comparison of robust median values. The method was adopted from methodological sources, published applications and the tools based on the computation system of R-project™ [10].

Results

Efficacy

The average exposure time (time between drug or placebo instillation and first micturition) was 168 ± 94.8 min in Group A, 219 ± 97.3 min in Group B, 127 ± 69.2 min in Group C and 108 ± 59.1 min in Group D. The difference between exposure time in Groups B and D was statistically significant.

When comparing parameters before and after treatment using conventional statistical methods (Kruskal–Wallis test), no statistically significant changes were observed within the groups. Comparing the difference between groups, a statistically significant difference in the bladder contractility index (BCI) parameter was observed. The difference in group A was significantly higher than the difference in Groups C and D, and the difference in Group B was significantly higher than the difference in Group D ($p = 0.0243$).

The results are summarized in Table 3.

Statistical significance was not found within the interval of 0.05–0.95 (the actual course of the probability distribution function does not correspond), but using robust median values with regard to large point deviations (outliers from the measured set of values), the authors focused on trends in selected parameters, evaluating changes in their median values over time.

As OAB is defined as a symptom complex, further analysis was focused on the data obtained from the bladder diary and self-assessment questionnaires. Comparison of the medians, using an analysis based on the mathematical gnostics, showed superiority of Group B over the other groups in the following parameters: number of urgency grade 3+4 episodes/72 h, number of leakage episodes/72 h, OAB-q total score and PPBC total score. Group D was superior to the other groups in respect of the number of nocturia episodes/72 h.

The results of the analysis using mathematical gnostics are summarized in Table 4 and Figure 1.

Table 3. Change in individual parameters before and after treatment analysed using conventional statistics (Kruskal–Wallis).

Variable	Group A	Group B	Group C	Group D	p	
Uroflowmetry						
Voided volume (ml)	-17.50 ± 117.39	-50.67 ± 175.38	-45.40 ± 115.27	-13.22 ± 107.53	0.9849	
Maximal flow rate, Q_{\max} (ml)	0.00 ± 11.02	-2.11 ± 10.45	0.20 ± 6.70	-1.44 ± 8.11	0.9667	
Postvoid residual (ml)	5.00 ± 10.80	1.11 ± 3.33	0.00 ± 7.82	2.22 ± 4.41	0.9367	
Pressure/flow study						
Cystometric capacity (ml)	20.80 ± 112.18	26.89 ± 189.98	-35.30 ± 71.12	21.89 ± 108.71	0.5860	
Compliance (ml/1 cmH ₂ O)	-2.23 ± 30.46	-18.99 ± 32.60	-6.23 ± 38.30	-36.49 ± 75.30	0.8171	
Maximal detrusor pressure during voiding, p_{\det} (cmH ₂ O)	5.60 ± 13.56	4.22 ± 20.74	4.89 ± 21.17	-8.50 ± 9.27	0.1144	
Bladder contractility index	25.00 ± 25.89	22.44 ± 46.71	-11.00 ± 44.61	-16.38 ± 22.02	0.0243	A > C, D B > D
No. of micturitions/72 h	-2.91 ± 6.95	-5.11 ± 9.75	-3.90 ± 8.89	-2.11 ± 5.80	0.6513	
Three day voiding diary						
Average voided volume (ml)	33.45 ± 46.12	-11.11 ± 21.40	7.80 ± 36.64	21.67 ± 67.99	0.1880	
No. of urgency grade 3 episodes/72 h	-0.18 ± 14.84	-2.56 ± 7.07	-1.30 ± 5.36	-4.00 ± 5.27	0.8154	
No. of urgency grade 4 episodes/72 h	0.55 ± 2.62	-3.33 ± 4.18	2.40 ± 5.36	0.78 ± 1.30	0.0683	
No. of leakage episodes/72 h	0.55 ± 2.88	1.56 ± 10.11	2.50 ± 6.43	0.89 ± 1.76	0.8100	
No. of nocturia episodes/72 h	-0.09 ± 1.97	-0.33 ± 2.18	-0.50 ± 1.84	-1.44 ± 3.84	0.9053	
OAB-q						
Total score	-17.36 ± 17.47	-19.00 ± 17.64	-6.80 ± 16.75	-13.11 ± 10.56	0.3201	
PPBC						
Total score	-0.45 ± 0.93	-0.67 ± 0.71	-0.30 ± 0.95	-0.33 ± 0.71	0.7990	

OAB-q = Overactive Bladder Questionnaire; PPBC = Patient Perception of Bladder Condition.

Table 4. Change in selected parameters before and after treatment analysed using mathematical gnostics.

	Group A			Group B			Group C			Group D		
	Before treatment	After treatment	Difference (%)	Before treatment	After treatment	Difference (%)	Before treatment	After treatment	Difference (%)	Before treatment	After treatment	Difference (%)
Three day voiding diary												
No. of micturitions/72 h	34.7	30	-13.5	32.5	29.4	-9.5	32.6	32	-1.8	32.5	30.4	-6.5
Average voided volume (ml)	174.3	192.5	10.4	200	201.9	1.0	142.2	149.2	4.9	144.1	151.5	5.1
No. of urgency grade 3 + 4 episodes/72 h	11.5	8.8	-23.5	26.5	5.4	-79.6	6.5	3.5	-46.2	11.2	7	-37.5
No. of leakage episodes/72 h	1.3	1.2	-7.7	3.8	1.8	-52.6	1.9	1.7	-10.5	0.96	2.38	147.9
No. of nocturia episodes/72 h	2.36	2.84	20.3	2.42	3.21	32.6	2.9	3	3.4	3.3	2.21	-33.0
OAB-q												
Total score	94.6	78.8	-16.7	103.6	76	-26.6	77.6	69.1	-11.0	101.4	85.8	-15.4
PPBC												
Total score	4.34	4.07	-6.2	4.74	3.89	-17.9	4.59	4.02	-12.4	5.05	4.48	-11.3

OAB-q = Overactive Bladder Questionnaire; PPBC = Patient Perception of Bladder Condition.

Safety

No serious adverse events were observed during the study. In total, six episodes of adverse events were reported during the study (two patients developed flu, one patient sinusitis, one patient hypertension, one patient hypercholesterolaemia and one patient a UTI). In only one instance (the episode of UTI) was the adverse event considered to be related to the study procedure.

Discussion

With US Food and Drug Administration approval, OnabotA it is becoming a widely used treatment modality for OAB patients who have failed non-invasive treatments. Randomized placebo-controlled studies have shown that OnabotA, administered by intramural injection into the bladder wall of patients with OAB, leads to a significant improvement in urodynamic parameters and quality of life [11]. However, intramural injection is invasive and painful, and necessitates instrumentation and anaesthesia.

This study evaluated the possibility of administering OnabotA using intravesical instillation. It builds on previous promising data by Petrou et al. [12], who used pretreatment with DMSO, which for decades has been used for intravesical instillation in patients with interstitial cystitis. The botulinum toxin molecule is relatively large and unlikely to cross the phospholipid bilayer lining the urothelium. Petrou et al. described the use of DMSO to disrupt of the urothelial layer and improve the transport of the botulinum toxin molecule into the suburothelial tissue [12]. This could potentially lead to a higher concentration of the intravesically administered agent. Despite the fact that the mechanism of action of DMSO is unclear, and controversy exists in regard to its effect on the glycosaminoglycan urothelial layer [13], this compound was included in the present study. No consistent effects of DMSO were observed on either OAB symptoms or urodynamic parameters.

This study compares both symptoms and objective urodynamic parameters. As OAB is a symptomatic diagnosis, and urodynamic parameters often do not correlate with a patient's perception of OAB symptoms, the primary goal of the

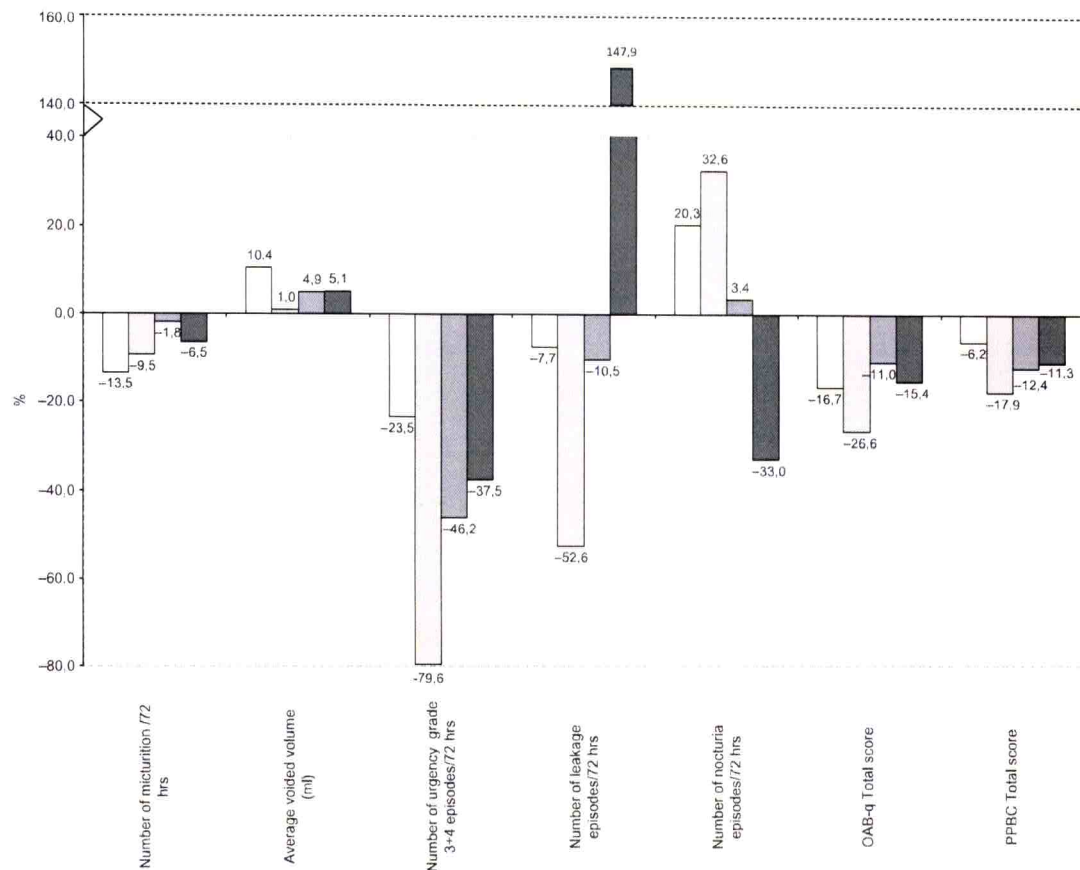


Figure 1. Change in the selected parameters before and after treatment. Results of the analysis using mathematical gnostics; bars represent individual treatment groups. OAB-q = Overactive Bladder Questionnaire; PPBC = Patient Perception of Bladder Condition.

treatment is to improve subjective parameters. This study documented that OnabotA, in combination with TC-3 hydrogel, suppresses urgency and overall OAB symptoms. This was evident from a reduction in the total number of severe urgency episodes and by decreased scores on the OAB-q and PPBC. These effects were more pronounced in a subgroup of patients who reported severe symptoms at the baseline pretreatment assessment.

No serious adverse events were observed during this study and only a single instance of UTI related to the treatment was recorded. No significant effects on the ability to empty the bladder (increase in PVR or decrease in BCI) were recorded. This compares favourably to clinical trials of intramural OnabotA injections, which report a 5% incidence of retention and up to a 43% incidence of increase in PVR [14]. This suggests that when compared to intramural injection, instillation could have a superior safety profile.

The documented effects of OnabotA on the lower urinary tract involve suppression of detrusor contraction by inhibition of the presynaptic release of acetylcholine, and suppression of sensory neurotransmission through mechanisms that may include modulation of mediator release from the urothelium and release of neurotransmitters and modulatory substances from afferent nerve terminals [15]. It has been suggested that the urothelium plays a key role in the bladder sensation and pathophysiology of OAB [16]. Therefore, it is reasonable to

assume that OnabotA does not have to permeate the urothelium to achieve a clinically relevant effect. The potential limitation of the clinical efficacy of intravesical instillation of OnabotA may stem from protein degradation by proteases, and proteinases in the urine or gradual dilution of the drug by urine [17].

The authors hypothesized that another significant issue could be the short exposure time. Embedding OnabotA into a hydrogel, which has been previously shown to facilitate a gradual release of drugs, could potentially address this issue. TC-3, which is part of the reverse thermal gelation gel family, has a high viscosity at body temperature and very low viscosity (fluid like) at 5 °C. Thus, the gel is delivered as a free-flowing liquid at low temperature and forms a gel within minutes of exposure to body temperature. This temperature-dependent viscosity characteristic allows for a simple instillation of the cooled gel into the internal human body cavities. The bulk, which is formed in the bladder, most probably remains there over several micturition cycles.

Kuo et al. used liposomes to facilitate the movement of the large OnabotA molecule through the urothelium, and showed a reduction in frequency episodes 1 month after treatment without an increase in PVR or increased risk of UTI [7]. However, it has to be noted that liposomes alone have been previously documented to have therapeutic effects in a detrusor overactivity model [18].

TC-3 gel has been synthesized as an inert drug delivery system; therefore, any therapeutic effect on the urothelium is unlikely. However, the authors recognize that this has not been confirmed by this study. Other potential limitations of this study are the sample size and heterogeneity among the study participants, especially the high severity of symptoms in patients who were randomized to the main treatment group (TC-3 + OnabotA). For this reason, mathematical gnostics – a method based on algorithms estimating true data values along with the characteristics of their uncertainty from small data samples – was used for statistical evaluation of the data. The gnostic theory of data is an alternative to statistics. It is intended for deriving data-treatment algorithms under practical circumstances when there are insufficient data items and the data are depreciated by the influence of strong uncertainty, and when a mathematical-statistical model of data and disturbances is not known or does not exist. Gnostic theory is not grounded on statistical preconditions. It forms a mathematical model of particular data uncertainty on the basis of a simple metrological axiom. The theory of small data samples then flows from the theory of particular data and from compositional law, determining the manner of particular data uncertainties' composition. Gnostic theory produces significantly robust data treatment algorithms [19].

The authors believe that this study provides justification for a large, multicentre clinical trial, comparing this new treatment to both placebo and TC-3 hydrogel alone. OnabotA is clearly an effective treatment for a very unfortunate subgroup of OAB patients. The minimally invasive method of drug delivery proposed in this study could become an alternative to intramural injection for a well-selected subgroup of patients. Eliminating the need to perform multiple injections using cystoscopy-guided delivery could broaden the patient population and improve their quality of life.

Acknowledgement

The authors wish to thank Travis Mann-Gow for his critical review and editorial assistance.

Declaration of interest

The authors declare no conflicts of interest.

This study was supported by the Ministry of Health, Czech Republic, conceptual development of research organization RVO-FNOs/2012.

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