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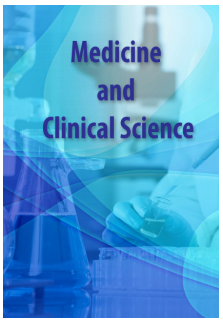

First In Human (FIH) clinical study for the evaluation of an ultrasound based botulinum toxin - A delivery system in subjects with Idiopathic Overactive Bladder (OAB)

Vseticka Jaroslav[1*], Geva Avner[2], Eftel Avi[2], Shick Maya[2], Rapp Filip[1], Drabek Frantisek[1] and Barbora Kopacova[1]

[1]*Department of Urology, Nemocnice Jablonec and Nisou, Czech Republic*

[2]*Vensica Medical Ltd, Israel*

Correspondence

Vseticka Jaroslav, MD

Head of Urology Department, Nemocnice Jablonec nad Nisou, p.o, Nemocnicni 4446/15 466 01 Jablonec nad Nisou, Czech Republic

Tel: +420-48-3345700

E-mail: vseticka@nemjbc.cz

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Abstract

Over active bladder (OAB) is defined by increased urinary incontinence, daily micturition, nocturia and urinary urgency. Present available treatments include, among others, oral medications and intravesical Botulinum Toxin A injections. Oral medications are associated with poor compliance, and Botulinum Toxin A injections are time consuming, invasive and are not financially rewarding for the urologists. Vensica Medical is developing an ultrasound based BonT/A delivery system that enables a simple, minimally invasive, and fast delivery of Botulinum Toxin A to the urinary bladder for the treatment of OAB. Vensica has completed the ultrasound based BonT/A delivery system First In Human study - Safety and Initial Performance of the ultrasound-based, needle-free BonT/A delivery system in Subjects with Idiopathic Overactive Bladder. The clinical study was a single center, prospective, open label study on 10 female OAB subjects that initiated on December 7th 2018 and completed on May 23rd. 2019 with full results. The results of study show no serious adverse events (device related or not) as well as improvement in several efficacy endpoints. The conclusion from the study is that the ultrasound based BonT/A delivery system is safe, easily operated by the physicians and accepted by the subjects. Further clinical studies should be conducted to further establish the efficacy of the system.

Clinical Trial Registry: NCT03874780

Introduction

Overactive bladder (OAB) is defined by the International Continence Society [1] as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection (UTI) or other obvious pathologies. OAB often has a chronic course and impacts adversely upon the health-related quality of life (QoL) of sufferers, who are more likely to be depressed and unemployed than age- and gender-matched controls. The economic costs of OAB run into the billions of dollars per year in healthcare expenditure and financial implications of lost productivity [2].

Several treatment options are available for OAB, including bladder and behavioural training, pharmacologic treatment, and surgical therapies. Oral antimuscarinics represent the mainstay of pharmacologic treatment for the management of OAB. They are recognized to be effective in the improvement of OAB symptoms and have a good safety profile. However, the incidence of antimuscarinic-induced adverse events is relatively high, and persistence rates with antimuscarinic therapy are low, with lack of efficacy and adverse events among the most frequent reasons for discontinuation [3].

Another treatment option is the local administration of Botulinum Toxin A that acts by inhibiting acetylcholine release at the presynaptic cholinergic junction. Starting in the late 1980s, the urology community has explored the use of botulinum toxin type A (BonT/A) to treat various urological pathologies. The efficacy of BonT/A in treating OAB has been supported by literature, and currently both American Urology Association (AUA) and European Urology Association (EAU) guidelines suggest that intravesical injection of BonT/A should be offered to subjects with urgency urinary incontinence [4]. Several clinical studies have shown significant improvement in OAB symptoms at a dose of 200 Units of BonT/A. In addition, two dose-finding studies with BonT/A, which used doses ranging 50-300 Units, showed that doses of 100 units and higher have resulted

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in significant improvement in OAB symptoms among study subjects [5]. Since this analysis was conducted, the FDA has approved a BonT/A pharmaceutical agent for the treatment of OAB – in 2013, the FDA has approved the first BonT/A-based drug for the treatment of OAB, named Botox™ (Allergan, Ireland).

Treatment with BonT/A for the alleviation of OAB symptoms is associated with side effects. In a meta-analysis conducted by Karsenty et al in 2008, which covered 18 large scale clinical studies with BonT/A for OAB, it was found that although safe and effective, treatment with BonT/A for OAB frequently causes injection site pain, procedure-related urinary tract infection (UTI) and mild haematuria [6]. Furthermore, BonT/A injections may cause retention and require self-catheterization by the subject. In addition, treatment with BonT/A by local injections to the bladder wall require unique settings, which by themselves pose a financial burden on the insurer [7].

Vensica Medical is developing the ultrasound based BonT/A delivery system, which includes a catheter and a console. The system is ultrasound based and enables needle-free, minimally invasive, safe, simple and fast delivery of BonT/A to the bladder wall. The procedure includes insertion of the designated catheter, drainage of the bladder, administration of the BonT/A and application of a therapeutic ultrasound, all by the same catheter. Vensica Medical has recently completed its First In Human (FIH) clinical trial with the ultrasound based BonT/A delivery system, whose aim was to assess the delivery system's safety and initial efficacy in subjects diagnosed with OAB by measuring the rate of device-related Serious Adverse Events (SAEs) at 7 days and 12 weeks post procedure. Initial efficacy was also measured by the completion of urinary diary, OAB-q Quality of Life questionnaire and Treatment Benefit Scale (TBS).

Methods

The study was conducted in the Urology Department at the Jablonec Nad Nisou medical center, Czech Republic. The study was approved by the local ethics committee (approval number LEK/7/2018/St dated September 5th, 2018) and the Czech State Institute for Drug Control (SUKL) (approval number sukls350138/2018 dated January 7th, 2019). Study population included female subjects between the age of 18-80 who had been previously diagnosed with OAB and who presented with symptoms of incontinence associated with OAB for ≥ 3 months prior to screening and who were non-responsive, non-compliant or intolerable to pharmacologic oral therapy (e.g., anticholinergic agents). Subjects were requested to sign an informed consent prior to their participation in the study; subjects who were mentally incompetent or unable to understand or comply with study procedure were excluded from enrollment. Women of childbearing potential were requested to have a negative urine pregnancy test prior to enrollment.

10 subjects were enrolled to the study between January and February 2019. Subjects were requested to complete at baseline a 5-day urinary diary and OAB-q Quality of Life questionnaire. Baseline Post Void Residue (PVR) volume was also measured in all subjects. All subjects were treated with the ultrasound based BonT/A delivery system. The first three (3) subjects were treated with a sub-clinical, low ultrasound power and low BonT/A dose in order to establish the safety of the procedure (safety establishment arm), followed by the treatment of the remaining seven (7) subjects with clinical ultrasound power and BonT/A dose (treatment arm).

All subjects were followed up for a period of 12 weeks after the procedure. Study visits took place 2, 6, and 12 weeks post procedure. Follow up phone calls took place 24 hours, 7 days and 4 weeks post procedure to establish peri-procedural safety. Prior to each scheduled visit, subjects were requested to complete a 5-day urinary diary. At each study visit, subjects also completed Quality of Life questionnaire (OAB-q) and Treatment Benefit Scale and underwent physical examination, adverse event and concomitant medication report and PVR determination.

Results

All 10 subjects completed the procedure and the 12-week follow up period.

Demographics

Parameter	Average (range, SD)	Notes
Age	64.0 (40.0-77.0, 10.7) years	
Weight	69.1 (52.0-83.9, 10.3) Kg	
Height	161.6 (152.0-171.0, 7.2) cm	
BMI	26.3 (20.8-31.3) Kg/m^2	
Smoker	0/10	
Alcohol consumption	2/10	1 drink of alcohol/ day
Childbearing potential	1/10	Negative urine pregnancy test

Table 1. *Subject Demographics at Baseline.*

Safety

No SAEs (device-related or -unrelated) were reported throughout the follow up period of 12 weeks post procedure.

Two (2) subjects experienced a single, mild bleeding at the first voiding after the procedure.

Efficacy parameters

Urinary incontinence was evaluated subjectively by the 5-day urinary diary, where subjects were requested to report the time of each incontinence episode throughout a 24-hour period, for 5 days.

Number of nocturia episodes was also evaluated by the 5-day urinary diary. Subjects were requested to report the time and volume of each nocturia voiding, using a designated measuring cup provided to them by the investigator.

Number of urinary urgency episodes was reported by the subject by the 5-day urinary diary, and was calculated by the number of episodes that the subjects has graded at least 3 in the urgency scale in the diary (ranging from 0 = no urgency, I felt no need to void but did so for other reasons to 4 = urge incontinence, I leaked before arriving to the toilet).

Positive Treatment Response. Each subject was requested to complete the TBS score, which consists of a single question regarding the degree of improvement in OAB symptoms after the procedure, and ranges between 1 = greatly improved to 4 = worsened. The study assessed the percentage of subjects who have a Positive Treatment Response on the TBS scale (a score of 1 or 2).

	Safety Establishment Arm			Treatment Arm		
	Baseline	6 weeks post procedure	12 weeks post procedure	Baseline	6 weeks post procedure	12 weeks post procedure
Value	1.2	1.3	1.2	1.1	0.8	0.3
Change from Baseline (%)		+8.3	0		-27.3	-72.3

Table 2. *Change from Baseline in the mean number of urinary incontinence/24h.*

	Safety Establishment Arm			Treatment Arm		
	Baseline	6 weeks post procedure	12 weeks post procedure	Baseline	6 weeks post procedure	12 weeks post procedure
Value	2.3	1.9	1.7	2.2	1.6	1.1
Change from Baseline (%)		-17.4	-26%		-27.3	-50%

Table 3. *Change from Baseline in the mean number of nocturia episodes.*

	Safety Establishment Arm			Treatment Arm		
	Baseline	6 weeks post procedure	12 weeks post procedure	Baseline	6 weeks post procedure	12 weeks post procedure
Value	20.3	14.3	15.3	24.0	22.3	17.6
Change from Baseline (%)		-32.1	-22.8		-2.8	-24.3

Table 4. *Change from Baseline in the mean number of Urinary Urgency Episodes/24 hours*

	TBS Positive Response Rate
Safety Establishment Arm	2/3 (67%)
Treatment Arm	5/7 (71%)

Table 5. *Change from Baseline in the mean number of Urinary Urgency Episodes/24 hours*

		Safety Establishment Arm (change in %)	Treatment Arm (change in %)
OAB-q – QOL score (improvement is presented by higher scores)	Baseline	53.3	59.3
	6 weeks Follow Up	80.8 (+52)	74.5 (+26)
	12 weeks Follow Up	85.6 (+60)	83.5 (+41)
OAB-q - Symptom bother score (improvement is presented by lower scores)	Baseline	60.8	55.0
	6 weeks Follow Up	32.5 (-47)	43.2 (-21)
	12 weeks Follow Up	21.7 (-64)	30.0 (-45)

Table 6. *Change from Baseline in OAB-q Quality of Life questionnaire throughout the study follow Up period*

The OAB-q questionnaire is a validated [8], multi-sectional questionnaire that assesses the patient's coping with overactive bladder symptoms. The questionnaire is commonly used in clinical research and clinical setting for this indication, and consists of the following 6 scores:

- Symptoms severity score
- Coping score
- Concern/worry score
- Social score
- Sleep score
- Quality of life score

These scores are further analysed to obtain two domains: Quality of Life total score (improvement is demonstrated in higher scores), and Symptoms Bother Score (improvement is demonstrated in lower scores). The questionnaire was not available in the Czech language, and was translated by the Sponsor of the study. The translation was then used in its unvalidated form.

Discussion

Overactive bladder is a troublesome disorder that affects both men and women, and causes a significant decrease in quality of life. Available treatments are limited to pharmaceutical agents, which are often poorly tolerated by patients, as well as intravesical injections of Botulin A toxin. The injections of BonT/A to the bladder wall requires anaesthesia, operating room settings and complete staff, and causes significant pain and discomfort for the patient. Vensica Medical developed the ultrasound based BonT/A delivery system in order to address the limitations and downsides of currently available treatments, and has completed the FIH clinical trial for the treatment of OAB in female subjects.

The study aimed at establishing the safety and initial performance of the ultrasound based BonT/A delivery system. Safety was assessed by the reports of adverse events throughout the study duration. During the study, no serious adverse events were reported by either the site staff or the subjects themselves (during phone calls and follow up visits). Therefore, this study has successfully demonstrated the initial safety profile of the ultrasound based BonT/A delivery system delivery system and has shown at least non-inferiority compared to available BonT/A injections to the bladder wall.

The First In Human study also examined the initial efficacy parameters. All parameters chosen for the study are well accepted in clinical trials in overactive bladder, and have been in clinical use for many years. Efficacy parameters relied mainly on the subject urination diary, given to each subject to complete for 5 days prior to each visit. All subjects fully completed the diary, with no missing data or partial completion. All secondary efficacy endpoints examined in this study showed improvement throughout the follow up duration and until 12 weeks post procedure. These findings are in line with the effect of the clinically available BonT/A injections to the bladder wall.

Urinary incontinence was assessed via the urinary diary. Aside from the improvement in the average number of incontinence episodes, a significant difference was measured between the safety establishment arm and the treatment arm. While the average number of incontinence episodes/24h remained generally unchanged in the safety establishment arm, there was a significant reduction in their number in the treatment arm (-72.3%), although both groups had the same average incontinence episodes at baseline.

Number of Nocturia episodes was assessed, and the results showed a significant improvement of both groups compared to baseline, and a greater improvement in the treatment arm compared to the safety establishment arm. When comparing these results to the clinical experience of commercially available BonT/A injections, the results obtained from the safety establishment arm are in line with those reported in the literature [9], thus further supporting the ultrasound based BonT/A delivery system's efficacy and mode of operation. The results obtained from the treatment arm, where a higher dose was used, are better (-50%), which are likely due to the increased dose.

Voiding urgency is another parameter assessed by the urinary diary. The mean urgency per 24h was moderately improved after treatment with the ultrasound based BonT/A delivery system, in both groups. However, the mean number of urinary urgency episodes per 24h, as reported by the subjects, has shown a more significant improvement after the treatment, with no difference between the safety establishment group and the treatment arm. These findings may be the result of the subjects' behavioural habits, where they tend to void more frequently and while feeling less urgency, in order to avoid any leakage later, or to avoid having to visit the restroom in a less appropriate time. This may also explain the only mild improvement in the overall number of daily micturition (data not shown).

The effect of the treatment on the subjects participated in the study, as determined by the TBS scale and the OAB-q questionnaires, was a positive one. Most subjects, in both groups, reported a beneficial effect of the treatment on their OAB symptoms. Given that these subjects had already had experience with available pharmaceutical treatments and/or intravesical injections of BonT/A, their positive attitude towards the treatment with the ultrasound based BonT/A delivery system is encouraging and supports the system's simplicity and tolerability by OAB patients. Further demonstration of the system's simplicity was obtained by the Ease of Use questionnaire, completed by the investigators after each procedure. The investigators found the system to be user-friendly, easy to operate and safe for use (data not shown).

Conclusion

The results of the study show that the system can be used safely, it is well tolerated by the subjects and is well received by the physicians. The initial assessment of the efficacy of the system shows it affects OAB symptoms at least as good as the available intravesical BonT/A injections, while offering a more cost-effective, less invasive and less painful route of administration. Since this was a safety trial, the ultrasonic activity of the ultrasound based BonT/A delivery system system was not exploited to its fullest potential of BonT/A delivery to the bladder wall. Vensica Medical believes that even better efficacy results may be achieved with higher acoustic intensities of the ultrasound based BonT/A delivery system. Further clinical investigations are also required in order to better determine the delivery system's safety profile in the general population, as well as to establish its efficacy.

Conflict of interest statement

The authors of this article do not have any conflict of interest among them.

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