296

Jabs C[1], Carleton E[2]
1. *Regina General Hospital, University of Sasktachewan,* ***2.*** *Regina Qu"Appelle Health Region*

EFFICACY OF BOTULINUM TOXIN A INTRADETRUSOR INJECTIONS FOR NON-NEUROGENIC URINARY URGE INCONTINENCE - A RANDOMIZED DOUBLE-BLIND CONTROL TRIAL

Hypothesis / aims of study

Non-neurogenic urinary urge incontinence (UUI) is a common quality of life disorder that becomes more prevalent with age. Standard treatment for UUI includes behaviour modification, pelvic floor exercises, anticholinergic medication, and less commonly, sacral neuromodulation. Unfortunately anticholinergic therapy is only moderately effective and causes bothersome side effects, particularly at higher doses. The objective of this study was to determine the efficacy of intradetrusor injection of botulinum toxin A (BTA) on non-neurogenic UUI.

Study design, materials and methods

The study was a prospective 12 month, randomized, double-blinded, partial cross-over design. Patients were either randomized to receive intradetrusor injection of 100u of BTA via cystoscopy or placed in a placebo control group that received intradetrusor saline injections. Women over 18 years of age with a confirmed diagnosis of idiopathic urge incontinence refractory to anticholinergic treatment were considered eligible for inclusion. Patients were recruited from the clinical practice of the lead author. The study research analyst randomized subjects using a random numbers table and the allocation was concealed in an envelope. An operating room nurse prepared the appropriate solution of either BTA or saline which was then brought into the operating room. The patient and surgeon were blinded until 6 months, at which time they were unblinded and the placebo group was offered BTA. All subjects were followed for the remaining 6 months. Evaluations were performed at baseline, 6 weeks, 3, 6, 9 and 12 months. The primary outcome was maximum capacity at cystoscopy (MCC); secondary outcomes included the results of the diary data (incontinence episodes (IE), daytime voids, and nocturia), 24 hours pad tests, 4 disease specific validated quality of life measures (Patient Perception of Bladder Condition, Incontinence Impact Questionnaire, Indevus Urgency Severity Scale and Urogenital Distress Inventory), as well as a subjective benefit assessment. Safety data included adverse effects, documented urinary tract infections (UTI), and need for self-catheterization.

To analyse between group differences (BTA vs. placebo) over time, difference scores were computed for the primary outcome (baseline compared to 24 weeks) and the secondary outcomes (baseline compared to 6 weeks, 12 weeks and 24 weeks) and compared using the Wilcoxon-Mann-Whitney *U* test. The subjective benefit assessment did not have a baseline score, therefore between group differences were analyzed at 6 weeks, 12 weeks and 24 weeks using the same test. The number of UTI was analyzed using a Chi-square. For all statistical tests 2-sided p values were used and alpha was set to 0.05.

Results

The results provided are the interim results up to 6 months for the first 20 subjects (11 BTA, 9 placebo) with a mean age of 64.5 years (range 46 to 84). A sample of 16 subjects per group was required to detect a mean difference of 50 ml in MCC between BTA and placebo at 90% power with a two-sided type I error of 5%. Recruitment has stopped at 21 subjects due to slow accrual.

There were no significant differences between groups at baseline for the primary or secondary outcomes. The results of the comparison between BTA and placebo over time, found a significant difference between groups in MCC and the mean difference between the two groups over time was 124.7ml. There were no significant differences found between groups for the diary data or quality of life scales, although some of the outcomes were approaching significance (see Table 1 for diary data). There were statistically significant differences between the groups subjective benefit assessment at all three time points (6 wk, 12 wk and 24 wk), with the BTA group having 6 subjects with a "*dry/complete response*" at 24 weeks (see Table 2).

There were 14 instances of UTI in the BTA group from baseline to 6 months and 8 instances in the placebo group (not significant). Four patients had a subjectively slower urinary stream and some urinary hesitancy following injection of BTA. Only one patient performed any self-catheterizations and all residuals were $\leq$ 200ml. Adverse effects were more common in those patients that received BTA (6) vs. placebo (3), respectively, including hematuria (1 vs. 1), pain (3 vs. 2), constipation (1 vs. 0) and a perioperative cardiac event (Takotsubo syndrome) (1 vs. 0).

Table 1: MCC & Diary Data outcomes: Comparison between groups over time

	BTA (n = 11)		Δ from B	Placebo (n = 9)		Δ from B	p value
	M±SD	Md	M	M±SD	Md	M	
MCC (ml)							
Baseline	495±204	525	-	423.9±177.3	380	-	-
24 Wk	559.1±223.2	525	64.1	363.3±85.6	380	-60.6	0.033*
IE							
Baseline	6.1±5.9	4.5	-	5.2±2.3	5	-	-
6 Wk	3.1±4.8	0	-3	4.7±2.6	6	-0.5	0.147
12 Wk	1.0±1.7	0.5	-5.1	4.1±3.4	3.3	-1.1	0.090
24 Wk	2.0±3.0	0	-4.1	5.3±5	4.3	0.1	0.098
Daytime							

voids							
Baseline	10.1±5	8.5	-	8.4±2.9	8	-	-
6 Wk	7.9±3.4	8.0	-2.2	8.4±3	9	0	0.080
12 Wk	6.8±2.4	7.5	-3.3	8.1±2.7	9	-0.3	0.063
24 Wk	7.4±2.8	7.5	-2.7	8.8±2.8	8.8	0.4	0.088
Nocturia							
Baseline	2.5±2.2	2.0	-	2.1±0.9	2	-	-
6 Wk	1.7±1.5	1.5	-0.8	1.8±1.2	1.5	-0.3	0.867
12 Wk	1.1±0.8	1.0	-1.4	2.1±1.6	1.3	0	0.104
24 Wk	1.1±0.9	1.0	-1.4	1.8±1.3	2.3	0.3	0.313

M (Mean) SD (Standard Deviation) Md (Median) * indicates statistically significant

Table 2: Subjective Benefit Assessment: BTA vs. Placebo

	BTA (n = 11)			Placebo (n = 9)			p value
	M	SD	Md	M	SD	Md	
6 Wk	2.4	1.2	3	3.4	0.9	4	0.035*
12 Wk	1.9	0.8	2	3.1	1	3.5	0.018*
24 Wk	1.6	0.8	1	2.7	0.9	3	0.018*

4= no change, 3= $\leq$ 50% improvement, 2= > 50 % improvement, 1= dry
M (Mean) SD (Standard Deviation) Md (Median) * indicates statistically significant

Interpretation of results

Botulinum toxin A was effective in improving UUI symptoms. The difference scores comparison between the two groups found a statistically significant difference in MCC. There was support for the efficacy of botulinum toxin A, with significant differences in subjective benefit assessment between BTA and placebo. Incontinence episodes, day time voids and nocturia were reduced from baseline and there was improvement in all quality of life scores although between group differences did not reach statistical significance. In the group receiving BTA, 6 of 11 patients had a complete response and were dry at 6 months after injection.

Concluding message

Botulinum toxin A intradetrusor injections were well tolerated and provide beneficial improvement in adults with non-neurogenic UUI resistant to anticholinergic medication.

Specify source of funding or grant	**none**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**Health Canada: Health Products and Food Branch #120486**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Regina Qu'Appelle Health Region: Research Ethics Board #08-03**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**