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EFFICACY OF BOTULINUM TOXIN A INJECTION FOR NEUROGENIC DETRUSOR OVERACTIVITY AND URINARY INCONTINENCE – A RANDOMIZED DOUBLE-BLIND TRIAL

Hypothesis / aims of study

Antimuscarinic medication is usually first line treatment of neurogenic detrusor overactivity (NDO) associated with spinal cord injury (SCI) or multiple sclerosis (MS). Concomitant bladder emptying is frequently accomplished by intermittent catheterization; however, patients may have an incomplete response to medication with persistent urinary incontinence. Side effects may limit their use despite the advent of newer long-acting anticholinergic agents with lower rates of side effects. Investigational agents such as capsaicin and resiniferatoxin that target sensory fibers are not widely applicable and invasive surgical procedures such as bladder myomectomy, intestinal augmentation, or urinary diversion may be the only alternative in some instances. Botulinum Toxin A (BoNTA) injections into the detrusor have been shown to provide significant improvement in patients with NDO, including those refractory to antimuscarinics (1); however, there is a paucity of randomized controlled trials of BoNTA reported in the literature (2). The aim of this study was to determine the efficacy of intravesical BoNTA on NDO in this group of patients that have urinary incontinence secondary to SCI or MS.

Study design, materials and methods

This was a prospective, multicentre, randomized, double-blind study of 57 subjects (34 male, 23 female), with a mean age of 42.8 years (range 32 to 50) with NDO secondary to either spinal cord injury (SCI) (n=38) or multiple sclerosis (MS) (n=19). Subjects were eligible for inclusion if they had urinary incontinence (minimum of one occurrence per day) despite current anticholinergic treatment. Following a 1-2 week screening period where baseline 3-day voiding diary and multichannel urodynamics (UDS) with subtracted detrusor filling and, when possible, voiding pressures, were established, subjects received one intravesical injection cycle of BoNTA, 300U, diluted with 30 cc of normal saline, or placebo (saline) with a flexible or rigid cystoscopic injection needle at 30 intra-detrusor sites, sparing the trigone. Subjects attended clinic follow-up visits at 6, 24 and 36 weeks. Follow-up evaluation consisted of UDS, subject questionnaires (the International Consultation on Incontinence Questionnaire (ICIQ) and Urinary Incontinence-Specific Quality of Life Instrument (I-QOL)), adverse event assessment, and a 3-day voiding diary completed prior to the visit. At week 36, all subjects were offered open label BoNTA (300U) intra-detrusor injections and further assessments took place at 48 and 60 weeks with voiding diary and questionnaires. The primary efficacy parameter was the frequency of incontinence episodes (IE) on 3-day voiding diary and secondary parameters were changes in UDS and questionnaires at 6 weeks. Sample size estimation was based on the following assumptions: at week 6 mean change from baseline of 0.75 IE, standard deviation (SD) of 0.85 IE, alpha 0.05, beta 0.20. To detect a difference of 0.75 between treatment groups in the mean change from baseline in the frequency of IE and assuming a 20% dropout rate, it was necessary to enrol 56 subjects (28 per group). Efficacy and safety analyses were conducted on an intent-to-treat basis. Continuous data was summarized using descriptive statistics; categorical data was summarized in frequency tables.

Results

57 subjects (28 BoNTA, 29 placebo) underwent injections. Treatment groups were similar at baseline with regard to demographics, urinary symptoms, and UDS findings. For the primary efficacy parameter, frequency of IE in the BoNTA group demonstrated marked and significant reduction versus placebo at 6 weeks that persisted up to week 36. For the secondary parameters, significant improvement of urodynamic parameters (detrusor volume at 1st detrusor contraction, volume at maximum detrusor pressure) in the BoNTA group was evident at week 6 and persisted to week 24. Subjects in the BoNTA group also benefited from an improvement in quality of life (based on I-QOL) through to week 36. Following open-label injection at 36 weeks subjects in both groups experienced significant improvements in diary related variables and quality of life questionnaires that persisted through 60 weeks. (The Table below shows the results summary.) Adverse events were similar between treatment groups. Mild transient upper body weakness was reported by 2 subjects in the BoNTA group.

		Detrusor Vol. at 1st Detrusor Contraction (median)	Vol. at Max Detrusor Pressure (median)	Frequency of IE		I-QOL Δ from BL (mean)
				Daily Freq (mean±SD)	% Δ from BL (median)	
BL	B	132.5 mL	200.5 mL	3.06±1.69	-	-
	P	124.5 mL	200.0 mL	4.03±2.36	-	-
Wk 6	B	357.0 mL**	490.0 mL***	1.31±1.25***	-57.1%***	19.52±22.93***
	P	200.0 mL	230.0 mL	4.76±2.91	12.5%	-2.23±13.24
Wk 24	B	200.0 mL**	328.5 mL*	1.56±1.52***	-47.5%***	16.27±22.72*
	P	130.5 mL	223.0 mL	3.98±2.71	0.0%	0.44±16.73
Wk 36	B	173.0 mL	299.0 mL	2.37±1.92*	-25.0%*	7.91±10.84*
	P	112.0 mL	208.0 mL	4.21±2.70	0.0%	-1.91±15.39
Wk 48	B	-	-	1.56±1.69§	-55.0%§	21.5±23.81§
	P	-	-	1.86±2.19§	-57.14%§	21.64±25.73§
Wk 60	B	-	-	1.43±1.21§	-50.45%§	15.36±20.98†
	P	-	-	1.54±1.82§	-66.25%§	16.55±21.13†

BL (Baseline), B (BoNTA), P (Placebo)

Treatment group comparisons: *p<0.05, **p<0.01, ***p<0.001

Compared to baseline: † p<0.01, § p<0.001

Interpretation of results

Intra-detrusor injections of 300U BoNTA provides significant and sustained improvement in UD parameters, diary related variables including reduced frequency of urinary leakage episodes in patients with NDO secondary to SCI or MS. Importantly, there is a corresponding significant improvement in patient reported quality of life. The improvements were persistent at 24 to 36 weeks following injection. Following open-label injection similar improvements in diary variables and QOL were seen in subjects previously randomized to placebo.

Concluding message

BoNTA injections into the detrusor are well tolerated and provide clinically significant and beneficial improvements in adults with NDO and incontinence refractory to antimuscarinics. These improvements were seen at up to 9 months following injection.

References

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What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Instiutional Review Boards from Sunnybrook Hospital, University Health Network, Dalhousie University, Jewish General Hospital, St. Luc Hospital, University of Manitoba, University of Calgary**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**