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Outcome of a Randomized, Double-Blind, Placebo Controlled Trial of Botulinum A Toxin for Refractory Overactive Bladder

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Abstract

Purpose—We determined the effectiveness of cystoscopic administration of botulinum-A toxin compared to placebo for the treatment of urinary incontinence in subjects with idiopathic overactive bladder.

Materials and Methods—Subjects were recruited from the Division of Urogynecology at the University of Rochester. Inclusion criteria were overactive bladder refractory to anticholinergic medications, multiple daily incontinence episodes and a 24hour pad weight of 100 gm or greater. Subjects with low leak point pressures, increased post-void residual volume or neurological etiologies were excluded from study. Subjects were randomized to placebo or to 1 of 2 doses of botulinum-A toxin. The detrusor was injected at 8 to 10 sites above the trigone. Evaluations were performed at baseline, and at 3 and 6 weeks after injection, and included bladder diaries, pad weights, quality of life questionnaires and urodynamic studies.

Results—A total of 22 subjects participated in stage 1 of this 2-stage study. We report on the outcomes of stage 1 of this study. Because stage 2 is still ongoing and investigators remain blind to the doses of botulinum-A toxin, the 2 botulinum-A toxin groups were combined for this report. There were no differences in mean baseline measurements between the 2 groups. Statistically significant improvements in daily incontinence episodes, pads changed per day and quality of life questionnaires were seen in the botulinum-A toxin group with no changes in the placebo group. No change in nocturia, daily voiding frequency, peak flow or detrusor pressure was seen in either group. Of 15 subjects 4 (26%) receiving botulinum-A toxin had a post-void residual volume of 200 cc or greater and 1 subject required intermittent catheterization. Four subjects experienced a urinary tract infection, 2 (13%) in the botulinum-A toxin group and 2 (28%) in the placebo group (not significant).

Conclusions—Botulinum-A toxin can significantly reduce urge urinary incontinence due to overactive bladder at 6 weeks. However, there is a risk of urinary retention requiring self-catheterization.

Keywords

botulinum toxins; urinary bladder; overactive; urinary incontinence; urge

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THE prevalence of urinary incontinence in the United States ranges from 3% to 14% with estimates ranging up to 40% for the elderly.[1] UUI is frequently caused by overactive bladder and currently the most effective pharmacological treatment for OAB includes anticholinergic medica-tions.[2] However, many patients do not respond to these medications or have significant side effects causing discontinuation and they experience persistent symptomatic UUI.

The effects of botulinum-A toxin on striated muscle are well documented in the neurology and plastic surgery literature.[3-8] Several studies including a recent randomized, placebo controlled trial have shown that BTX is effective for neurogenic detrusor overactivity.[9-11] Recent uncontrolled case series have shown significant reductions in incontinence and improvement in urodynamic parameters in subjects with idiopathic OAB.[12-16] We describe the out comes of a randomized, double-blind, placebo controlled trial of BTX for the treatment of severe OAB.

MATERIALS AND METHODS

This study was performed at the University of Rochester, Rochester, New York. The institutional review board approved this protocol and the trial was registered with the National Institutes of Health clinical trials website before study initiation. This study includes 2 stages, with stage 1 a 6-week randomized, placebo controlled trial and stage 2 a9-month randomized trial of 2 doses of BTX without a placebo control (fig. 1). In this report we describe the results of the completed stage 1. Because stage2 is not yet complete investigators have not been unblinded to the dose of BTX. Thus, the data for the 200 U and 300 U BTX groups were combined for this analysis. The decision to limit the placebo controlled portion to the 6-week stage 1 was based on the concern supported by institutional review boards that it would be unethical to withhold an effective treatment from the placebo group for longer than 6 weeks.

Subjects

Subjects were recruited from the Urogynecology clinic beginning in May 2005. Patients presenting to this clinic completed a 3-day bladder diary, performed a 24-hour pad weight, and underwent urinalysis and multi-channel urodynamics including PVR measurement. Subjects had to demonstrate multiple (more than 2) daily incontinence episodes occurring with urge on a 3-day bladder diary and have a 24-hour pad weight greater than 100 gm. Subjects were not required to have urodynamic proven detrusor overactivity. Because it is not uncommon to find OAB and stress incontinence together, we allowed subjects with coexisting severe OAB and mild stress incontinence to enter the study. To minimize the impact of the stress component of the leakage and to eliminate subjects with intrinsic sphincter deficiency, subjects could not have a cough leak point pressure less than 100 cm H_2O. At least 1 anticholinergic medication and behavioral modifications must have failed in subjects before they entered the study. Subjects had to demonstrate a willingness and ability to perform self-catheterization, and have a negative urine culture. Subjects were excluded from study if they had any known neurological condition, gross fecal incontinence or an absent detrusor contraction on pressure flow. All anticholinergic medications were stopped at least 10 days before study entry.

Randomization and Blinding

Subjects and clinicians were blinded to study assignment. A random number generator was used to randomize subjects in blocks of 6 to placebo or BTX. Study assignments were assigned via sealed, sequentially numbered opaque envelopes. Serial evaluations were performed for 6 weeks after injection when subjects were unblinded to medication assignment but not dose. Subjects receiving placebo ended the study. Those receiving BTX proceeded onto stage 2 and these evaluations are still ongoing.

Because of the risk of prolonged urinary retention with the use of BTX, the protocol called for adjusting 1 or both doses of BTX if there were multiple instances of urinary retention. Study safety parameters called for subjects to be unblinded to medication dose if they had symptomatic urinary retention requiring intermittent self-catheterization 3 weeks after the study injection. No formal values for urinary retention were used to determine if ISC was necessary. The decision to perform ISC was based on subject symptoms. If subjects complained of discomfort or any other symptoms of retention and had a PVR greater than 100 cc, they would be instructed to begin clean intermittent catheterization. PVRs were obtained in all subjects at the 6-week visit or earlier if the subject complained of any symptoms suggestive of retention.

Procedures

BTX administration—After informed consent was obtained all subjects demonstrated the ability to perform ISC. The bladder was filled with 40 cc 2% lidocaine and 1% viscous lidocaine administered to the urethra for 20 min-utes. A 14Fr operating sheath with 12 degree cystoscope and a 22 gauge injection needle (Olympus, Center Valley, Pennsylvania) was inserted into the bladder which was filled with enough saline to smooth the bladder mucosa (approximately 100 cc). Study investigators were blinded to medication preparation. BTX was reconstituted in 3 cc saline according to manufacturer instructions (Allergan, Irvine, California). Three cc saline were used as placebo. Staying superior to the trigone and medial to the ureteral orifices, the detrusor muscle was injected with approximately 0.2 cc study solution per site at 10 to 12 sites along the posterior bladder wall. The detrusor was injected in parallel lines approximately 1 cm apart beginning 1 cm above the interureteral ridge. Three to 5 injections per line were performed with approximately 1 cm between the injections. At the time of study design there was no consensus concerning ideal volume of dilution of BTX, the volume of each injection or the sites of injection. We used this volume of dilution and volume of injection with good effect in our pilot study and elected to use the same for this study.[12] After the injections were complete subjects emptied their bladders and were discharged home.

Urodynamic evaluations—Urodynamics were performed according to ICS standards using a Laborie Aquarius XLS (Laborie Medical, Williston, Vermont).

Pad weight measurements, bladder diaries, UDI-6 and IIQ-7—These evaluations were performed before injection and at each point in a typical manner as described elsewhere.[12] While subjects were required to have multiple IE per day associated with urge to enter the study, all incontinence episodes were counted when calculating IE per day.

Complication screening—At all interactions subjects were assessed using a verbal questionnaire for evidence of adverse effects including problems emptying the bladder, new urinary leakage, interval urinary tract infection, systemic muscle weakness, focal weakness in muscles proximal to the bladder, dry mouth, increased constipation, fecal leakage, dyspareunia or other side effects.

Surveillance evaluations—Using the verbal questionnaire for complication screening, subjects were contacted by telephone for the first 3 days after injection to screen for any signs of adverse effects due to the BTX. Subjects reporting any signs suggestive of an adverse event such as retention were asked to come to our office for evaluation. Subjects were evaluated in our outpatient clinic 3 and 6 weeks after injection. To minimize the risk of urinary tract infections compromising incontinence data, 5 days before all clinic evaluations subjects started a 3-day course of 500 mg ciprofloxacin or Bactrim®reg; DS twice daily. The 3-day bladder diary was started 4 days before the study visit and the 24-hour pad weight was performed the day before the visit. At all evaluations, subjects completed bladder diaries, 24-hour pad

weights, and quality of life and complication screening questionnaires. At all clinic visits urine was checked for evidence of infection by urine dipstick, and if suggestive for a UTI it was sent for culture. Data for a given visit were discarded if a culture proven UTI was found at that visit. At the 6-week evaluation CMG and micturition studies with PVR measurement were performed.

Outcomes—Primary outcome measures were the number of incontinence episodes per 24 hours as determined from a 3-day bladder diary, and scores on the UDI-6 and IIQ-7.[17] Secondary outcomes included 24-hour pad weights, number of pads used per 24 hours, 24-hour voiding frequency, diurnal urinary frequency and nocturia as determined from the 3-day bladder diary; MCC, volume of first uninhibited detrusor contraction and the presence of stress leakage on CMG; and value of detrusor pressure at peak flow, peak urine flow and PVR on micturition study. Diurnal urinary frequency was determined as described by Brown et al.[18]

Statistical Analysis

Based on values and standard deviations from our earlier study, an a priori power analysis indicated that we needed 7 subjects per group for a 90% power and a significance of 0.05 to detect a 40% improvement in IE per day at 6 weeks.[12] We assumed a 10% dropout rate. Analysis was done on an intent to treat basis. Statistical analysis was performed using SAS® version 8.02. A repeated measures ANOVA using a mixed measures model was performed on each outcome measure except for the urodynamic outcomes which only had 2 time point variables. A post hoc analysis of the mixed measures model was performed to compare changes at each point for each outcome variable. Student's paired t test was used to determine significance of differences for each urodynamic parameter. For all statistical tests 2-sided p values were used and alpha was set to 0.05.

RESULTS

A total of 22 subjects were recruited. All 22 of these subjects completed stage 1 and no subjects were excluded from this analysis. No subjects were prematurely unblinded for this analysis. Seven subjects received placebo and 15 received BTX. Figure 2 shows the CONSORT (Consolidated Standards of Reporting Trials) flow diagram of subject enrollment and retention of subjects.

Mean (range) age, parity and body mass index for all subjects was 66 (41 to 85), 2.75 (0 to 7) and 32 (23 to 45), respectively, with no significant differences between the 2 groups. At least 1 anticholinergic medication as well as behavioral modification failed in all subjects. Four subjects in the BTX group and none in the placebo group had a prior procedure for stress incontinence. Table 1 shows mean baseline values for the study outcomes for the placebo and BTX groups. The high pad weights and number of daily incontinence episodes reflect the severity of the incontinence in these subjects who typically wore incontinence briefs rather than pads. Eleven subjects had mixed incontinence, 3 (42%) from the placebo group and 8 (53%) from the BTX group (not significant). No subject had a leak point pressure less than 131 cm H_2O. Fifteen subjects demonstrated detrusor overactivity on CMG. Of the 7 subjects that did not show uninhibited detrusor contractions on CMG 2 received placebo and 5 BTX (not significant).

Figure 3 shows the graphic results of the repeated measures ANOVA for selected outcomes. The differences reflected in these graphs are statistically significant at all points as demonstrated in tables 2 and 3.Table 2 shows changes in values from the mixed measures model over time in the 2 groups for each outcome variable undergoing the ANOVA. The base line values reported are slightly different from those in table 1 because these are the values of the least squares mean obtained from the mixed measures model. We saw clear statistically

significant differences over time in the BTX group for IE per day, IIQ-7 and UDI-6 scores, 24-hour pad weight, pads per day and nocturia with no changes in the placebo group. We also saw a significant time and treatment interaction for the IIQ-7, UDI-6, IE per day and 24-hour pad weight. We saw no difference in the number of voids per day or diurnal voiding frequency, although voids per day trended toward significant reduction in the BTX group.

Table 3 shows comparisons of the least square means from the mixed measures model between the 2 treatment groups at each point. They demonstrate statistically significant improvements in the BTX group compared to the placebo group for all 3 primary outcomes, 24-hour pad weight and pads used per day at each point. There were no differences between the groups with regard to voids per day, diurnal voiding frequency and nocturia.

There was a statistically significant increase in PVR in the BTX group from a baseline of 25 to 107 cc (p [H11022]0.01) with no significant change in the placebo group (30 to 27 cc, NS). We found no statistically significant differences in MCC, volume of first uninhibited detrusor contraction, peak flow or detrusor pressure at peak flow.

We saw few complications in either group. One subject receiving placebo experienced gross hematuria after injection requiring overnight hospitalization for continuous bladder irrigation. The hematuria began immediately after the saline injection was completed. Subsequent cystoscopy demonstrated gross hematuria flowing from the left ureteral orifice. Followup evaluation of the upper tracts and cytology showed ureteral varicosities as the probable etiology. Two subjects (13%) in the BTX group and 2 (28%) in the placebo group (not significant) experienced UTIs with 3 of the 4 occurring within 5 days of injection. De novo stress incontinence did not develop in any subjects. One subject reported an increase in the frequency and severity of her stress urinary incontinence. She also reported an increase in participation in physical and social activities concurrent to the reduction in UUI.

Four (26.6%) subjects receiving BTX experienced PVR values greater than 200 cc at the 6-week evaluation. One subject was symptomatic and required intermittent catheterization at 3 weeks. This subject had received 200 U BTX. The remaining 3 subjects with increased PVR reported a significant reduction in incontinence and denied any symptoms related to increased PVR. They were not unblinded and will continue to be followed for 9 months.

DISCUSSION

Refractory idiopathic detrusor overactivity continues to be a significant problem for clinicians treating women with urinary incontinence. Because treatment options are limited and often invasive, an effective minimally invasive alternative would be an attractive option for this population.

This study demonstrated clinically and statistically significant improvement in objective measures of volume and frequency of incontinence as well as validated quality of life measures. Mean improvement for these measures ranged from 40% to nearly 70% and persisted for 6 weeks. While it would have been informative to continue the placebo arm beyond 6 weeks, given the severity of the incontinence in these subjects, ethical concerns of withholding an effective therapy from these subjects prevented followup evaluations beyond 6 weeks in the placebo cohort. Of the 7 placebo subjects 6 went on to receive BTX for incontinence.

Our results are similar to those of a recently published randomized, placebo controlled trial using BTX for OAB.[19] Sahai et al randomized 34 male and female patients with idiopathic detrusor overactivity to 200 U BTX or placebo. However, they saw improvements in measures of frequency and urgency as well as MCC and volume of first detrusor contraction. Because we had fewer subjects in the placebo group and had 7 subjects without a detrusor contraction

on CMG, we were likely underpowered to detect changes in these secondary outcomes. Of these 3 outcomes only MCC trended toward an improvement in the BTX cohort from 336 to 378 cc but this was not statistically significant (p [H11005] 0.08).

It is not clear why we did not detect an improvement in urinary frequency in the BTX group. Compared to the Sahai et al cohort our population had much higher baseline IE per day (7.94 vs 4.98), IIQ-7 (54.54 vs 18.31) and UDI-6 (49.23 vs 10.75) scores, respectively. This suggests that our group had more severe OAB at baseline and perhaps 6 weeks was too soon for learned voiding behaviors to change in our cohort with severe OAB. In addition, a third of the Sahai et al cohort continued on anticholinergic medications during the study whereas none of our subjects were taking anticholinergic medications during the study.

Several authors have reported on the effectiveness of BTX for idiopathic OAB in nonrandomized case series.[12-16] Some also reported an incidence of retention requiring clean intermittent catheterization.[13,15] We saw minimal complications during this study and the complications are consistent with those reported by other authors. Given the mechanism of action of BTX it is not surprising that some experienced urinary retention. Importantly all of these subjects reported high satisfaction with outcomes and the 1 subject requiring ISC stated that she preferred ISC and reduced incontinence to the incontinence before BTX injection. We compared the 4 subjects with increased PVR to the other 11 subjects without increased PVR and could not identify any clinical or urodynamic predictors for urinary retention after BTX injection. Sahai et al saw a similar incidence of increased PVR but a higher rate of subjects requiring intermittent catheterization.[19] This may be because we only instituted ISC for subjects with symptomatic retention. Because of the prolonged nature of the retention and the risks associated with prolonged catheterization, it seems prudent for patients considering this treatment to learn ISC before injection.

We identified 4 subjects who experienced urinary tract infections during the first 6 weeks after injection, 2 in each group. This rate seems a bit high for such a brief followup period but may be because some of these UTIs were self-reported and we do not have laboratory confirmation of the infection. Given that some subjects travelled more than 2 hours to participate in this study and were often treated by local physicians, it is not surprising that we could not confirm all UTIs with laboratory data. Prudence would dictate reporting any antibiotic therapy as likely UTI. There was no significant difference in the rates between the placebo and BTX groups, indicating that this overall group may be at increased risk for UTI at baseline. Alternatively because we regularly administer antibiotics before each visit to reduce the likelihood of a UTI compromising incontinence data, we likely artificially decreased the rate of UTIs diagnosed. Further studies are needed to determine if there is an increased risk of UTI with this therapy.

There remains significant controversy concerning the ideal administration of BTX. While our study demonstrated that our injection technique will effectively treat OAB for 6 weeks, the ideal dose, dilution of BTX, site of injection, depth of injection, number of injections and frequency of injections all remain controversial and unsettled. A detailed discussion of these issues is beyond the scope of this report and further studies are needed to conclusively answer these questions.

There are limitations to this study. We failed to comprehensively monitor the number of patients who were potential subjects for this study but who declined to participate and, thus, possibly introduced a selection bias that could limit our external validity. Anecdotally the reasons that potential subjects declined to participate included difficulty with completing the 9-month followup, declining to learn the self-catheterization technique or the desire to address other medical issues before participation. It is possible that subjects and investigators were

effectively unblinded by the presence or absence of the expected drug effect of BTX as data were collected at the 3 and 6-week visits before unblinding.

We did not require detrusor overactivity on urodynamics for study inclusion and, in theory, this may have led to the inclusion of subjects without OAB. Because urodynamic testing often fails to show uninhibited detrusor contractions in women with OAB due to detrusor overactivity, we judged this inclusion criterion too stringent.[20] Because all subjects demonstrated multiple daily episodes of urge associated incontinence on a 3-day bladder diary it is unlikely that they did not have OAB as a significant component of their incontinence. We also allowed some subjects with mixed incontinence in the study. As shown in table 1 the subjects demonstrated multiple daily episodes of urge incontinence on 3-day bladder diaries and had high pad weights. Because no subject in either group had a cough leak pressure of greater than 131 cm H_2O, effectively eliminating leakage due to intrinsic sphincter deficiency, almost all incontinence in these subjects was due to OAB. In addition, because BTX injections in the detrusor should not affect the stress component of the mixed incontinence, the inclusion of these subjects would lead to underestimating the effect of BTX on urge incontinence, thereby strengthening our findings of the effectiveness of BTX. We did not formally screen for neurological etiologies beyond obtaining a patient history and a routine urogynecologic examination. It is unlikely that a significant number of subjects had an undiagnosed neurological condition that was severe enough to cause neurogenic detrusor overactivity without causing any other significant neurological symptoms.

CONCLUSIONS

BTX is an effective short-term treatment for refractory idiopathic OAB but there is a risk of urinary retention. Further studies are needed to establish the appropriate dose of BTX, appropriate concentration, site of injection in the bladder, depth of injection or frequency of repeat injections based on this study.

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Abbreviations and Acronyms

BTX, botulinum-A toxin
CMG, cystometrogram
IE, incontinence episodes
IIQ-7, Incontinence Impact Questionnaire
ISC, intermittent self-catheterization
MCC, maximum cystometric capacity
OAB, overactive bladder
PVR, post-void residual volume
UDI-6, Urogenital Distress Inventory
UTI, urinary tract infections
UUI, urge urinary incontinence

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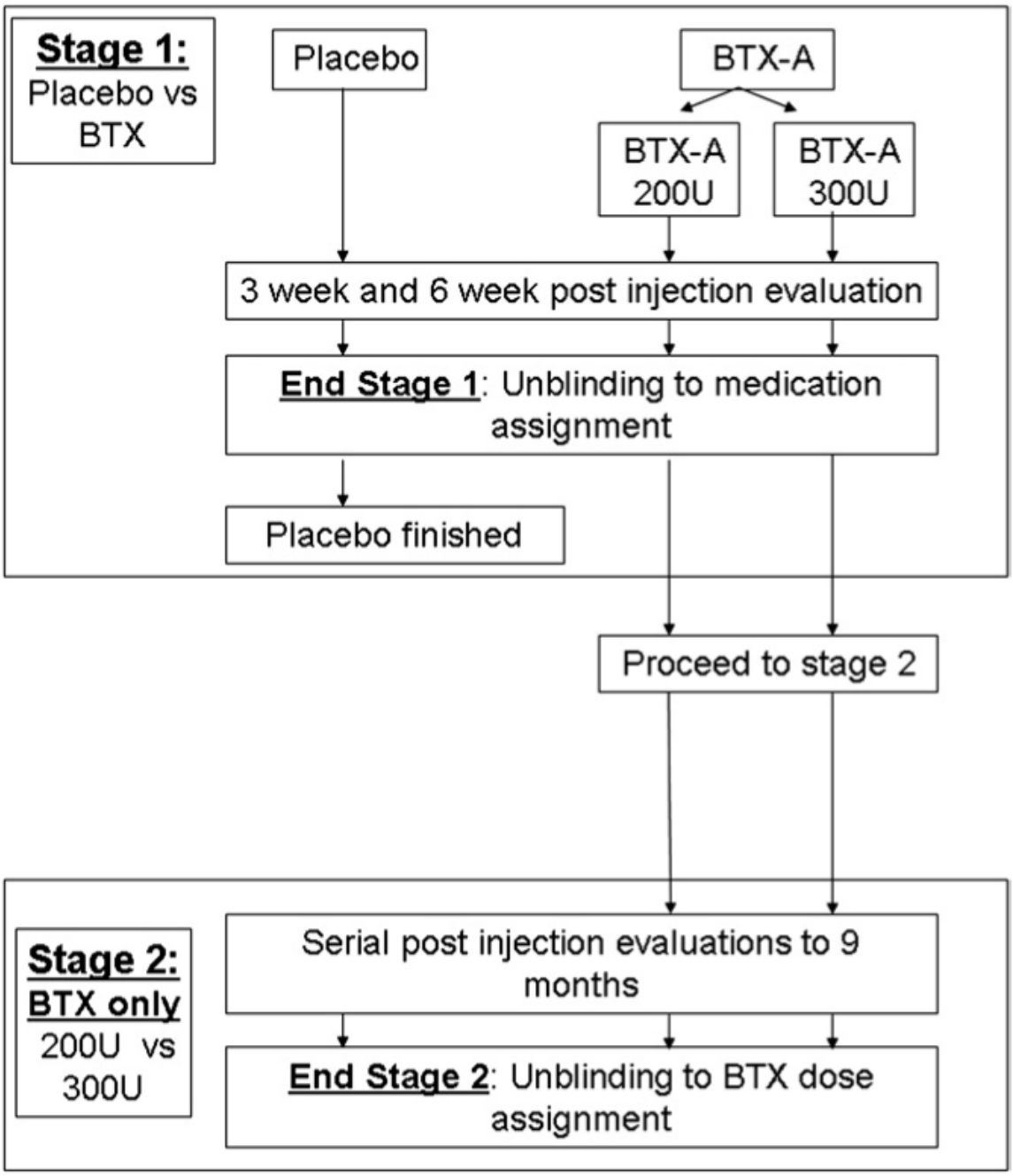

Figure 1.
Two-stage study design

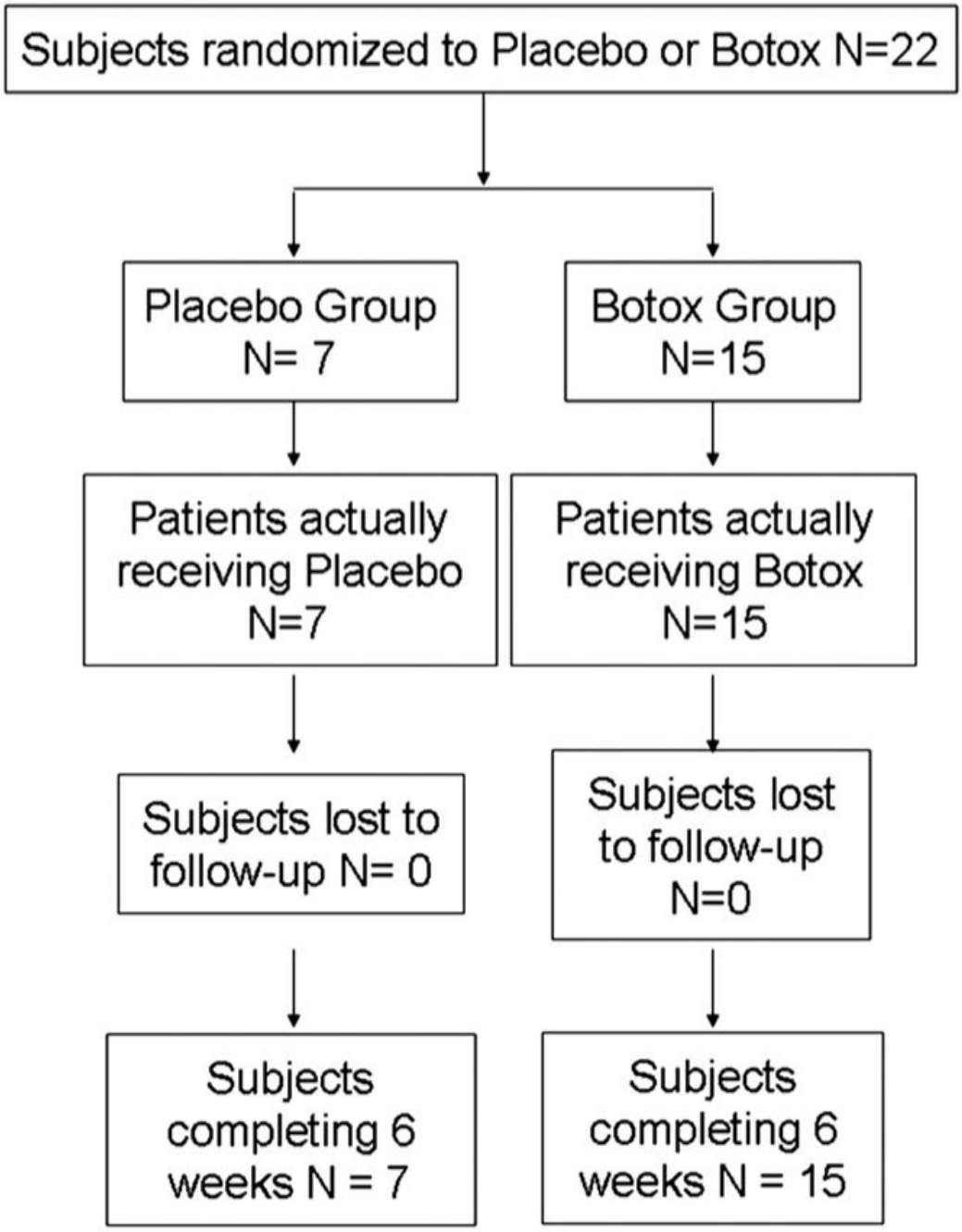

Figure 2.
CONSORT flow diagram of enrollment and study period. Botox, BTX.

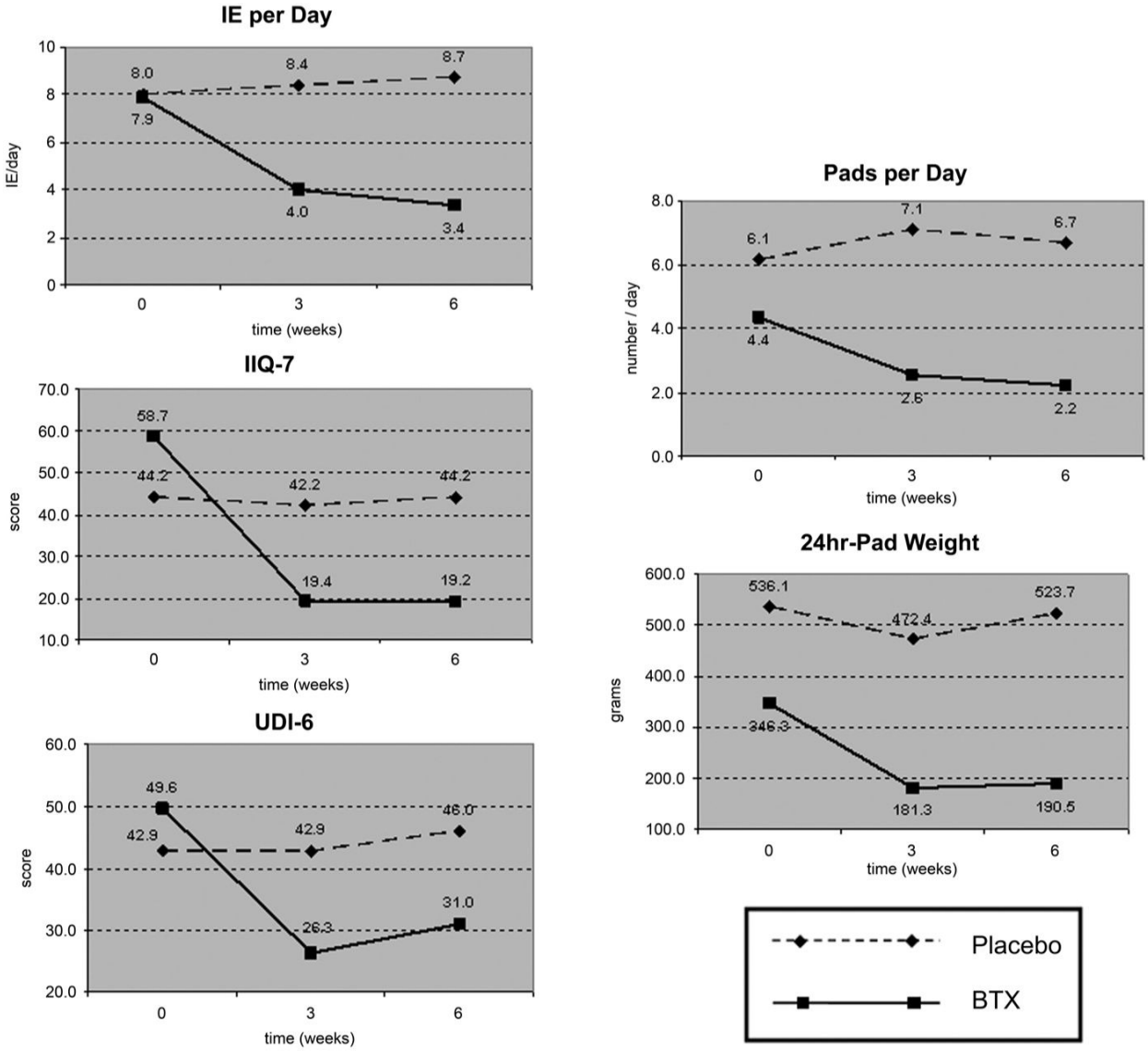

Figure 3.
BTX vs placebo over time for primary and secondary outcomes

Table 1

Baseline of placebo and BTX for primary and secondary outcomes

	Mean (SD)		
	Placebo	**BTX**	**p Value**
Incontinence episodes/day	8 (5.1)	7.9 (3.6)	0.96
IIQ-7 score	44.2 (23.0)	59.4 (23.2)	0.17
UDI-6 score	42.9 (8.9)	52.2 (11.5)	0.07
Pads/day	6.1 (3.0)	4.4 (1.9)	0.11
24-Hr pad wt (gm)	536.1 (306.8)	364.1 (274.7)	0.20
Voids/24 hrs	11.1 (5.1)	10.5 (3.0)	0.75
Diurnal voiding frequency	4.8 (1.8)	4.3 (1.3)	0.48
Nocturia	1.8 (2.0)	1.9 (1.0)	0.87
Max cystometric capacity (cc)	254.3 (120.9)	336.1 (112.1)	0.14
Peak flow (cc/sec)	20.5 (14.7)	19.5 (9.1)	0.85
Detrusor pressure at peak flow (cm H_2O)	48.7 (27.1)	47.8 (26.3)	0.96
Vol of 1st uninhibited contraction (cc)	183.2 (111.3)	258.8 (145.7)	0.34

Table 2

Change from baseline at 3 and 6 weeks, and time/treatment interactions for primary and secondary outcomes

							Time/Treatment Interaction	
	Baseline	3 Wks	% Change From Baseline	p Value	6 Wks	% Change From Baseline	p Value	F Value	p Value
IE/day:								5.93	>0.01
Placebo	8.0	8.4	4.8	0.78	8.7	9.3	0.59		
BTX	7.9	4.0	-49.0	>0.01	3.4	-57.5	<0.01		
IIQ-7:								9.1	>0.01
Placebo	44.2	42.2	-4.6	0.81	44.2	0.0	1.00		
BTX	58.7	19.4	-67.0	>0.01	19.2	-67.3	<0.01		
UDI-6:								4.2	0.02
Placebo	42.9	42.9	0.0	1.00	46.0	7.4	0.67		
BTX	49.6	26.3	-47.0	>0.01	31.0	-37.5	>0.01		
24-Hr pad wt:								0.91	0.41
Placebo	536.1	472.4	-11.9	0.50	523.7	-2.3	0.97		
BTX	346.3	181.3	-47.6	0.01	190.5	-45.0	0.02		
Pads/day:								5.89	>0.01
Placebo	6.1	7.1	15.5	0.21	6.7	9.0	0.47		
BTX	4.4	2.6	-41.4	<0.01	2.2	-49.0	<0.01		
Voids/day:								0.23	0.8
Placebo	11.1	10.6	-4.0	0.69	10.3	-6.8	0.50		
BTX	10.5	9.2	-12.6	0.07	9.2	-12.2	0.08		
Diurnal voiding frequency:								0.44	0.65
Placebo	4.8	4.6	-3.4	0.70	5.0	3.3	0.72		
BTX	4.4	4.0	-9.1	0.19	4.0	-7.7	0.27		
Nocturia:								0.78	0.46
Placebo	1.8	1.8	3.1	0.86	1.5	-15.7	0.37		
BTX	1.9	1.5	-20.8	0.05	1.4	-24.4	0.02		

Table 3
Difference in treatment between BTX and placebo at each interval

	Baseline	3 Wks	6 Wks
IE/day:			
Placebo	8.0	8.4	8.7
BTX	7.9	4.0	3.4
p Value	0.95	0.02	>0.01
IIQ-7:			
Placebo	44.2	42.2	44.2
BTX	58.7	19.4	19.2
p Value	0.18	0.04	0.02
UDI-6:			
Placebo	42.9	42.9	46.0
BTX	49.6	26.3	31.0
p Value	0.34	0.02	0.04
24-Hr pad wt:			
Placebo	536.1	472.4	523.7
BTX	346.3	181.3	190.5
p Value	0.10	0.02	>0.01
Pads/day:			
Placebo	6.1	7.1	6.7
BTX	4.4	2.6	2.2
p Value	0.14	>0.01	>0.01
Voids/day:			
Placebo	11.1	10.6	10.3
BTX	10.5	9.2	9.2
p Value	0.76	0.40	0.53
Diurnal voiding frequency:			
Placebo	4.8	4.6	5.0
BTX	4.4	4.0	4.0
p Value	0.49	0.30	0.15
Nocturia:			
Placebo	1.8	1.8	1.5
BTX	1.9	1.5	1.4
p Value	0.86	0.60	0.91