

DIFFERENT TYPES AND DOSAGES OF INTRADETRUSOR BOTULINUM TOXIN A INJECTIONS IN SPINAL CORD PATIENTS: A SINGLE CENTRE EXPERIENCE IN 15-YEARS FOLLOW-UP.

Hypothesis / aims of study

No long-term data have been reported in patients affected by neurogenic detrusor overactivity (NDO) switching type of botulinum toxin A (BoNTA) and/or different dosages (1,2). In this retrospective study, we report our results in patients with NDO secondary to spinal cord lesion (SCL) treated with alternative types and dosages of BoNT/A with or without concomitant use of antimuscarinics over 15-year follow-up.

Study design, materials and methods

We selected only adult SCL patients undergone first BoNTA from October 1999 to October 2001 who were managed by intermittent catheterization regimen.

Baseline 3-days bladder diary (BD) and urodynamics were pulled out from database. Further urodynamic data were extracted only in case of failure. The BoNTA failure was defined in case patients reported at least one daily episode of urinary incontinence at BD before 3 months post-injection. The duration of efficacy was defined as the interval (months) between the previous BoNTA and the patient's scheduling for re-treatment. Pre-new injection 3-days BD, concomitant antimuscarinic therapy, type and dosage of BoNTA previously used, were collected as well. Moreover, before re-injection, the number of YES response at the question concerning whether subject reached 6-month of dryness without antimuscarinics, was picked out. During follow-up two different toxins were used: AboBoNTA (Dysport®, Ipsen Ltd, Slough, UK) at dosage of 500 and 750 IU ; OnaBoNTA (Botox®, Allergan Inc, Irvine, CA, USA) 300 IU and 200 IU. This latest dosage was started in March 2013 since the approval in Italy. After injections, individuals taking antimuscarinics were asked to progressively reduce the dosages up to the interruption if urinary continence was achieved. Patients were also advised to gradually start again or increase oral drug before re-injections. The following baseline variables for long-term BoNTA response were considered: age > 40 years; SCL > 3 years; traumatic lesion; female gender; tetraplegia; complete lesion; use of antimuscarinics; compliance < 20 ml/cmH₂O; Pdetmax > 40 cmH₂O; urinary incontinence episodes ≥ 4 per day. Data analysis were performed by the software STATGRAPHICS XVII (StatPointTechnologies, Warrenton, VA). The F-test (ANOVA) test was used to compare the mean duration of efficacy amongst the four BoNTA treatments. Significance was *p value* ≤ 0.05. Multiple regression analysis was performed to describe the relationship between effectiveness and all the baseline variables taken into account. Models have been fit containing all of combinations from 0 to 5 variables. Evaluation of result was done by the adjusted and unadjusted R-Squared values. Fitted model was used to make prediction.

Results

A total of 60 SCL patients, mean age of 38.5 years before first BoNTA injection, were included. Of those, 45 (75%) were males, 16 (26.6%) tetraplegic and 38 (63.3%) with complete SCL. All subjects reported 2-6 daily episodes of urinary incontinence at their baseline BD. According to our results, patients were sub-grouped as following: "never failure" (NF) only patients who did not fail with BoNTA; "occasional failure" (OF), individuals who had at least one but not successive failure; "consecutive failure" (CF) subjects with continuing BoNTA ineffectiveness. Overall 32/60 (53.4%) were defined as NF; 16 (26.6%) OF and 12 (20%) CF. A total of 822 BoNTA detrusor infiltrations were performed over mean follow-up of 15.6 years. In particular, OnaBoNTA 300 IU, AboBoNTA 750 IU and OnaBoNTA 200 IU were used respectively 315 (38.3%), 261 (31.8%), 138 (16.8%) times. AboBoNTA 500 was used only in 108 cases (13.1%). Results on the mean duration of efficacy for each BoNTA among the three groups are reported in table 1. No statistically significant differences were found between treatments. (*p*= 0,6295). Twenty-nine NF (90.6%) and 12 (75%) OF individuals were still in follow-up. Overall 5 patients, 3 in NF and 2 in OF group, voluntarily stopped BoNTA and underwent bladder augmentation. The percentage of YES response, whether they reached 6-month of dryness without concomitant antimuscarinics at each injection, shifted from 19% (AboBoNTA 500 IU) to 29 % (OnaBoNTA 300 IU) in NF, whereas in OF from 18% (AboBoNTA 500 IU) to 25% (OnaBoNTA 300 IU). In particular, only 5 NF patients (15.6%) maintained continence up to 6-month without the use of antimuscarinics at each injections.

Considering the OF group, 25 failed injections were documented: 8 (32%) with OnaBoNTA 300 IU, 8 (32%) with AboBoNTA 750 IU, 5 (20%) with OnaBoNTA 200 IU, and 4 (16%) with AboBoNTA 500 IU. Five out of 16 subjects (31.25%) defeated twice nonconsecutively, while 2 (12.5%) had three discontinuous failures. In all cases of BoNTA ineffectiveness, the following re-injection was managed by the same toxin and dosage previously used. Nine out of 12 CF patients (75%) had failure at the first injections. A total number of 42 injections was performed, of which 35 (83.3%) consecutively failed. Different toxin and/or dosage were used only after the second successive failure. The number of BoNTA consecutive failures ranged from 2 to 4. Ten out 12 CF patients never interrupted and/or reduced antimuscarinics after each BoNTA injection. Regarding the baseline urodynamic findings, 8 (25%) NF, 5 (31.2%) OF and 9 (75%) CF patients showed low compliance (< 20 ml/cmH₂O), respectively. Overall in our sample, no patient with normal compliance at baseline became low compliant at further urodynamics during follow-ups. No variables from urodynamic, clinic and demographic baseline characteristics were found significantly predictive for long-term response.

Never Failure				Occasional Failure				Consecutive Failure			
Type of BoNTA	N° of injections	Mean (± SD)		Type of BoNT/A	N° of injections	Mean (± SD)		Type of BoNT/A	N° of injections	Mean (± SD)	
OnaBoNTA 300 IU	202	8,39356 (±2,64007)		OnaBoNTA 300 IU	96	8,33854 (±2,87502)		OnaBoNTA 300 IU	17	2,42941 (±0,828225)	
OnaBoNTA 200 IU	96	7,97917 (±2,08619)		OnaBoNTA 200 IU	42	7,61905 (±2,97922)		OnaBoNTA 200 IU	0	-	
AboBoNTA 500 IU	79	8,27215 (±2,3572)		AboBoNTA 500 IU	22	7,1 (±3,29372)		AboBoNTA 500 IU	7	2,47143 (±0,694537)	
AboBoNTA 750 IU	162	8,50309 (±2,24542)		AboBoNTA 750 IU	81	7,87654 (±3,01821)		AboBoNTA 750 IU	18	2,5 (±0,840168)	
Total	539	8,33488 (±2,39163)		Total	241	7,94481 (±2,98689)		Total	42	2,46667 (±0,795005)	

Interpretation of results

A high percentage of SCL patients (70.7%) are still in follow-up over 15 years. These individuals reported mean clinical efficacy of around 8 months. To the best of our knowledge this is the first study showing the absence of statistically significant difference between BoNTA treatments in a long-term follow-up (1,2). As a matter of fact, our findings showed that the switch with different toxins (OnaBoNTA vs AboBoNTA and viceversa) did not represent a determinant factor for improving the clinical response, considering that in our OF group, patients previously failed with one type of BoNTA, subsequently responded at the same toxin and dosage, previously administered. Whereas, in CF group, patients failed despite the attempt of switch treatment. Moreover, only a low percentage of 6-months dryness was achieved without oral drugs. Although no predictive factors for long term response were detected, CF patients showed a higher percentage of low compliance at baseline urodynamics. However, on the basis of overall these considerations reported above, should subjects be advised to continue BoNTA treatment up to 15-years? Indeed, our findings support that an appropriate patients' counselling is mandatory considering the need of chronic concomitant use of antimuscarinics, the time duration of dryness, the changeability of the responsiveness amongst each treatment and the risk of occasional BoNTA ineffectiveness. Those information should be discussed with patients at the time of the first injection and mainly repeated over time. However, we are conscious that one limitation of the present study was not having followed up the impact on QoL during 15-years.

Concluding message

Long-term repeated intradetrusorial injections for NDO secondary to SCL did not increase failures or favor refractoriness, independently to the BoNTA treatment and switching over time. Further studies are needed to determine which conditions such as deterioration of urinary tract function, impact on QoL and/or worsening of the health status may strongly recommend to discontinue the long term use of BoNTA. Moreover, further cost-analysis are mandatory comparing BoNTA treatment to other options for NDO in order to justify the continuative use of BoNTA in follow-up longer than 15 years. Thus, recommendation and international consensus must address clinicians about the appropriate counseling in the long-term follow-up. In particular, clear criteria should provide the minimum time/months of dryness, with or without antimuscarinics, the role of urodynamic investigation, and how or when switching BoNTA.

References

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