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LONG-TERM FOLLOW-UP OF REFRACTORY NEUROGENIC DETRUSOR OVERACTIVITY PATIENTS WITH ENGLISH BOTULINUM TOXIN A: ONE SINGLE CENTRE EXPERIENCE

Hypothesis / aims of study

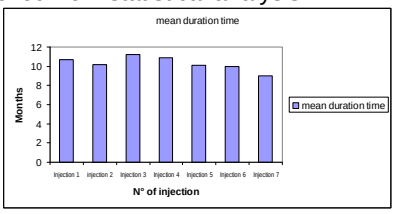
Botulinum-A toxin (BoNT/A) has proven to be a safe and effective therapy for a variety of somatic and autonomic motor disorders. In urologic field, its use is indicated when antimuscarinic medications, first line treatment for NDO, was ineffective to decrease incontinence episodes or caused intolerable side effects. A recent study do not find any significant changes in detrusor cell junction before and after BoNT/A injection, so in the detrusor muscle axonal regeneration probably does not play a focal role. The effect of a fast paralysis however is evident in detrusor muscle, objectively and subjectively, within 3-4 days to 2-3 weeks after injection and the efficacy of treatment lasts for a relatively long period, up nearly one year. Therefore the complete mechanism by which BoNT/A acts and loses its efficacy in detrusor muscles is still unclear. The use of BoNT/A in the treatment of NDO is increasing as well as the year of follow-up and consequently the number of re-treatment. But only few studies in literature take into considerations the possible develops of a drug resistance particularly in patients who undergone multiple treatments, moreover this few studies had a relatively short follow-up. We present here a long-term experience on a large homogeneous population of one single centre with the use of only English Botulinum Toxin type A (dysport®) in the treatment of refractory NDO in order to detect a possible reduction of BoNT/A efficacy and duration.

Study design, materials and methods

Between September 1999 and December 2005 we treated with dysport® injection 199 Spinal Cord Lesioned (SCL) patients with NDO resistant to conventional antimuscarinic therapy. All patients were evaluated with clinical examination, urine analysis and videourodynamic at baseline, 3, 6, and 12 months after each treatment, as well as with Visual Analogue Scale (VAS) and bladder diary checked for one week before each videourodynamic evaluation. Clean intermittent catheterisation (CIC) to empty the bladder was performed by all patients also before injection. We used 1000, 750, 500 I.U. of dysport® at the begin of our experience, and after we used mainly 750 otherwise 500 I.U. Detrusor muscle injections were performed in 20 sites under cystoscopic guidance, trigone and bladder neck sparing. dysport® was diluted in 20 ml 0,9% NaCl and 1 ml of solution was injected for each site. Patients were asked to reduce gradually, till completely suspension, their antimuscarinic medication over the first week till the third week after injections. During each follow-up visit all subjective and objective parameters were analyzed and when these data deteriorated substantially the patients were asked to return gradually to their antimuscarinic therapy till reach full dosage, and after we scheduled for re-injection. Outcome measures included: frequency of urge urinary incontinence episodes collected by bladder diaries, changes in urodynamic parameters such as maximum cystometric bladder capacity (MCBC), Reflex Volume (RV), bladder compliance, pads, condoms and antimuscarinic drugs consumption, short and long-term side effects and quality of life measured with VAS scale. These parameters were evaluated before, and at 3, 6 and 12 months after each re-treatment in order to detect any changes over time. Statistical analysis was performed with ANOVA test to compare the change in urodynamic parameters before and after each treatment. The ANOVA test was also used to compare the differences in the urodynamic changes and in duration time between the three dysport® dose. The unpaired t-test for trend was used to compare the mean duration time of each re-injection. Wilcoxon test was also used to compare the changes in VAS score and in bladder diary after each re-injection. Moreover we used Spearman's correlation coefficient to correlate the results of bladder diary and the efficacy duration time after each treatment.

Results

The mean age was 42.5 years (range 18–74 years), mean follow-up was 48 months (range 16-91 months).There were not statistically significant difference in efficacy duration time between three dysport® dose treatments (p>0,05). The difference between the intervals of injections is not statistically significant (p>0,05), only 2 patients had from 8 to 12 treatments, these patients were removed from statistical analysis.



The changes in urodynamic parameters (MCBC, RV, bladder compliance) improved significantly after treatment compared with baseline values (p<0,05), there were not statistically significant changes in the improvement of these parameters after each treatment (p>0,05) and in relation with dysport® dose. Twenty patients out of 199, 15 after first injections and 5 after repeated treatment respectively, showed poor clinical improvement. In these patients despite the increase of cystometric capacity we observed the appearance of an urodynamic pattern of reduced compliance without overactive detrusor. Nine out of these 20 patients underwent to augmentation cystoplasty. Other 11 went back to sovrapubic tapping. Others 3 out of 187 responders patients asked after three injections a definitive solution, so they were submitted to posterior sacral roots rizothomy with Brindley implant into anterior roots. These 3 patients had had some difficulties to recovery electromicturition. We did not observed any short term main complication as ematuria or de novo vesico-urethral reflux, but we observed, as we already reported, hyposthenia in 5 patients who were treated with high dose of intravesical BoNT/A injections (1000 IU dysport®), this supralesional weakness was transient,

disappearing 2 to 4 weeks after injection. There were a significant reductions in incontinence episodes frequency, pads/condoms and anti-cholinergics use in the first 4 weeks after each treatment and for a period strictly correlated with efficacy duration time ($p < 0,05$). Because of study facility we divided the patients in four subgroups on basis of mean duration time of each treatments. We have found 39 out of 199 (19,5%) patients with a mean duration time of efficacy after each injection > 12 months (very good responders), 80 out of 199 (40,2%) with mean duration time of treatment between 10 and 12 months (good responders), 60 (30,5%) patients with < 10 months (responders), and 20 (10%) patients < 6 months (low responders).

Interpretation of results

A series of data have been published in the last 5 years about Bont/A treatment for neurogenic lower urinary tract dysfunctions. In neurourological field, particularly for SCL patients, we indicate a long-life treatment for mainly young people without clear data about long-term clinical results and its impact on detrusor muscle. Even if recent published data seems to show that Bont/A injections do not determine istological changes on bladder muscle wall, and another study demonstrated that there were no differences about inflammation and oedema between bladder of patients with spinal cord injury with and without BoNT/A injections, these data are concerning short follow-up, 1 or 2 injections with a mapping system. The absence of ultrastructural changes could not exclude a long-term effect of toxin on the detrusor especially following repeated injections. In our series we identified different groups of patients based on their clinical outcome and VAS scale. There were about 20% of patients who showed a very good outcome after each injection (clinical duration time>12 months), 40,2% with a good response (mean duration time between 10 and 12 months), 30,5% with a normally response (<10 months), and 10% of low responders patients (<6 months). But we can not able to explain this different behaviour, the majority of non-responders demonstrated this refractivity within first injection, and the recent findings that there is major fibrosis in the bladder wall of non-responders patients could confirm this clinical observation that a pre-existing fibrosis could reduce the efficacy of botulinum injection. But statistical analysis on whole population confirmed that the lasting time of clinical efficacy is constant for each re-treatment.

Concluding message

Few studies reporting data about English toxin, with this study we demonstrated the long term efficacy and safety and high level of patients satisfaction using dysport®, moreover this efficacy is maintained during the time. Although the long-term effects of chronic treatment with botulinum toxin remain unknown. Longer follow-up and well designed studies are necessary in patients on maintenance therapy to define clinical beneficial as well as possible side-effect of prolonged therapy.

References

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HUMAN SUBJECTS: This study was approved by the Florence, Local Ethical Committee and followed the Declaration of Helsinki Informed consent was obtained from the patients.