Research Paper ■

A Double-blind Placebo-controlled Cross-over Study on the Effects of Botulinum Toxin Type A on Upper Limb Disorders

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Abstract. Botulinum treatment has been proven to be a promising treatment for many dystonic and spastic disorders. Apart from correction of posture and pain relief, functional testing is an important part of pre - and post-treatment assessment. We report results and dilemmas of using two assessment scales in a double-blind, placebo-controlled cross-over study on 10 patients with upper limb motor disorders. While the improvement on the Arm Function Test (AFT) after the Botulinum session was not statistically significantly higher than after placebo, the difference in favour of the treatment was much more evident on the 0-5 self-assessment scale. We believe that AFT is not sufficiently sensitive or at least not superior to simpler global scales, and that measurement of focal disability does not entirely clarify functional changes after treatment with Botulinum Toxin.

Dvojno slepa kontrolirana navzkrižna študija učinkov botulina A na bolezni zgornjih udov

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Izvleček. Zdravljenje z botulinom se je uveljavilo pri različnih boleznih z distonijo ali spastičnostjo. Poleg izboljšanja drže in lajšanja bolečine je funkcijsko testiranje poemmben vidik ocenjevanja izida zdravljenja. Poročamo o rezultatih in dilemah pri dveh ocenjevalnih lestvicah, ki smo jih uporabili v dvojno slepi s placebom kontrolirani navzkrižni študiji na 10 pacientih z gibalnimi boleznimi zgornjih udov. Izboljšanje na funkcijskem testu roke (AFT) po zdravljenju ni bilo statistično značilno večje v primerjavi s placebom, razlika v prid zdravljenja pa je bila mnogo jasnejša na samoocenjevalni lestvici 0-5. Menimo, da AFT ni dovolj občutljiv oziroma ni ustreznejši od preprostejših globalnih lestivc, ter da merjenje lokalnih zmanjšanih zmožnosti ne razjasni vseh funkcijskih sprememb po zdravljenju z botulinom.

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Introduction

Botulinum toxin (BTX) is one of the most potent neurotoxins known. It is a microbial protein that exists in several serotypes, from A to G.[1] For now, two antigenically distinct serotipes (BTX-A in BTX-B) are available for clinical practice.[2] BTX acts as enzyme at the presynaptic membrane to cleave three polypeptides that are essential for exocytosis (synaptosomal associated protein SNAP-25, vesicle associated protein – VAMP, and syntaxin). Different BTX types cleave different polypeptides and block acetylcholine release at the neuromuscular junction, which is in turn responsible for its therapeutic action to relive dystonia, spasticity and related disorders.

Recently, three review articles explored the efficacy of BTX therapy in different neurological conditions. The authors concluded that it is efficient therapy for cervical dystonia; probably effective in the treatment of focal limb dystonia, laryngeal dystonia, blepharospasm and tremor; and possibly effective in the treatment of hemifacial spasm.[3] It is also an effective in the treatment of spasticity.[1] However, there is controversy about its efficacy in the treatment of autonomic disorders and pain syndromes.[4]

Most of the existing studies on the efficiency of BTX therapy addressed the question of clinical improvement of the muscle tone as defined by reduction of spasticity or dystonia in patients.[5] There are some studies that showed inconsistent functional benefits from the therapy.[6,7] However, the functional consequences of the therapy remain unclear despite the fact that the functional issues are often a major focus of the rehabilitation programmes,[8] which are usually complex and include many different elements.[9]

Upper limb abilities presented by patients with disabled upper extremity can be divided into passive and active functions. Passive functions relate to the tasks preformed by the non-affected arm, whereas active functions include tasks that the subject performs with the affected limb.[8] Active function can be actually seen at as the capacity to move the body or its parts actively and can range from simple active movements to a complex movements and even more complex actions.[10]

As already mentioned, besides the clinical improvement the treatment with BTX also implies functional improvement. The functional goals include improvement of active and passive function, reduction of pain associated with passive mobilisation (in post-stroke patients) and painful spasms, improvement of hygiene, and prevention of contractures.[11] Consequently, estimation of functional outcome after BTX therapy is very important, and it might be actually more important than the clinical improvement itself.[12] One other important point is the sensitivity and specificity of functional tests used in assessment of the functional state of the upper extremity after BTX therapy.[13,14]

We present a double-blind placebo-controlled cross-over study that focused on the functional improvement after the BTX therapy measured by the medical professionals, as well as on the impact of the therapy from the patients' personal perspective. Patients with spasticity and/or dystonia of different aetiology were included, because the aim of the study was to test the functional efficacy of BTX therapy regardless of the cause of the treated condition.

Methods

Subjects

Ten patients with upper limb motor impairment, spasticity and/or dystonia, after stroke, encephalitis or cerebral palsy (six male and four female) were included in the study. Each patient gave an informed consent before entering the study.

Assessment tools

Two assessment scales were used: Arm Function Test (AFT)[14] and Self-assessment of Functional Improvement (SAFI). The former evaluates functional ability of the affected arm using seven graded tasks: (1) Use both hands to open jar; (2) Use both hands to rule a line; (3) Use affected hand to pick up and release 5 cm cylinder; (4) Use affected hand to pick up and release 1.25 cm cylinder; (5) Use affected hand to drink water from glass; (6) Use affected hand to comb hair; (7) Use affected hand to open and close clothes peg. Every task is scored either as 1 (capable of execution) or 0 (incapable of execution), so the overall score range is 0-7. The later test is a subjective self-assessment tool of functional improvement which quantifies the patient's perception of changes in the functional status of the affected hand. The 6-point scale is: (0) no functional improvement, (1) insufficient functional improvement, intermediate grades (2, 3, 4), (5) excellent functional improvement. The patients' response on this scale is assumed to show a faithful representation of their own perceptions of change in hand function.

Botulinum Toxin

BTX-A (Dysport) was used in the study: 500 units (U) of Dysport were diluted in 1 ml of saline so that 0.1 ml contained 50 U. One application site or, in the case of larger muscles, two application sites were used for BTX-A infiltration.

Study design and statistical analysis

No interventions in the rehabilitation programmes were preformed – physio- and /or occupational therapy programmes remained the same before, during and after the study. All patients were assessed by the same neurologist, Parkinson's disease nurse and occupational therapist on six occasions at one-month intervals (Table 2). The patients' responses were recorded on new assessment sheets on each occasion without referring to previous results. At day one, the patients were clinically examined and assessed using AFT. At every subsequent visit, besides clinical examination and AFT, SAFI was also administered. Cross-over was done at visit 4 unless the patient still reported benefit of the therapy. If there was still a benefit of the botulinum toxin, the cross-over change was done after the benefit wore-off (Table 1). At the second visit after starting the treatment, some patients could opt for a top-up if there was no effect or the effect was mild and unsatisfactory. Only conditions with defined patterns and selected muscles were treated and fixed dosages were injected (Table 2). Injection points were defined by an electromyographic atlas.[15]

Table 1 Study design.

Visit	Day	Description
1	0	clinical examination, AFT, BTX/placebo, video recording
2	30 ± 3	clinical examination, AFT, SAFI, video recording
3	60 ± 6	clinical examination, AFT, SAFI, video recording
4	90 ± 9	clinical examination, AFT, SAFI, cross-over, BTX/placebo, video rec.
5	120 ± 12	clinical examination, AFT, SAFI, video recording
6	150 ± 15	clinical examination, AFT, SAFI, video recording

Table 2 Sites of application of Botulinum Toxin Type A and dosages used in the study.

Muscle	Dosage
Flexor digitorum superficials (FDS)	50 U
Flexor digitorum profundus (FDP)	50 U
Flexor carpi ulnaris (FCU)	75 U
Flexor carpi radialis (FCR)	75 U
Biceps brachii (BIC)	150 U
Brachioradialis (BR)	150 U
Pronator (PRO)	100 U
Extensor digitorum communis (EDC)	150 U
Opponens pollicis (OPP)	75 U

Despite the cross-over design, we analysed the data using simple nonparametric matched-pairs comparisons between placebo and BTX difference scores. We opted for this approach for the

following reasons: because the study design minimised the possibility of carry-over effect, because we followed the authoritative advice not to test for carry-over,[16] because the groups were balanced so adjusting for period effect would have been meaningless,[16] and because the data were closer to ordinal then being of truly quantitative nature. For testing the scale difference scores, we used the exact Wilcoxon matched-pairs signed-rank test, while for dichotomised data (score improvement vs. no improvement) we used the exact McNemar test. Data analyses were performed using SPSS for Windows 15.0 software (SPSS Inc, Chicago, IL, 2007).

Results

The demographic and clinical characteristics of the patients are summarized in Table 1. The mean age of the patients was 31.1 years (SD 14.3 years). They all had long-term spasticity, on average for 10.8 years (SD 6.6 years). Two of the patients had spasticity because of cerebral palsy; the other patients had spasticity acquired later on in the life (one patient after bench meningoencephalitis, one patient after head trauma, one after neurosurgical extirpation of haemangioma, the rest of the patients had spasticity after CVI). Among those with acquired spasticity, four patients had left-sided hemiparesis and four had right-sided hemiparesis.

Table 3 Demographic and clinical data on the patients.

Patient	Age	Gender	Handedness	Diagnosis	Duration (years)*	Muscles treated
1	16	male	right	Right-sided spastic-dytonic hemiplegia; Dyskinesias	14	BIC, FCU, FCR
2	43	male	right	Right-sided spastic hemiplegia	20	BIC, BR, FDS, FDP
3	17	male	right	Cerebral palsy; Spastic-dystonic syndrome	17	BIC
4	15	female	right	Cerebral palsy; Spastic paresis	15	PRO, FCR, FCU
5	46	male	right	St. after CVI; Left-sided spastic hemiplegia	9	BIC, FDS, FDP
6	46	female	right	St. after CVI; Left-sided spastic hemiplegia	5	FCZ, FCR, OPP
7	31	female	right	St. after head trauma; Left-sided spastic hemiplegia	0	FDP; FDS; AP, BR; BIC
8	18	male	right	St. after bench meningoencephalitis; Right-sided spastic hemiplegia	3	FCU, FCR, FDP, FDS
9	51	male	right	St. after CVI; Right-sided spastic hemiplegia	3	EDC
10	28	female	right	St. after operation of haemangioma; Left-sided spastic hemiplegia	0	BIC, PRO, FCR, FCU, FDP, FDS

* Duartion of symptoms before therapy.

The AFT scores increased more after BTX therapy (by 0.4 on average, range 0-2) then after placebo (by 0.1 on average, range 0.1), but the difference was not statistically significant ($P=0.500$). On the other hand, the difference in SAFI scores in favour of BTX was statistically significant (mean improvement 2.8, range 0-5; vs. mean improvement 0.6, range 0.3 under placebo; $P=0.016$).

Neither of the scores worsened in any patient either after BTX treatment or after placebo. The tests on dichotomised data confirmed the results obtained with the original scores: 3 patients improved after BTX vs. 1 after placebo regarding AFT ($P=0.500$), and 8 patients improved after BTX vs. 2 after placebo regarding SAFI ($P=0.031$).

Discussion

The results of our study confirmed the beneficial effect of Botulinum Toxin Type A for treatment of spasticity and dystonia in upper limbs. However, the main aim of our study was to clarify functional benefit in the affected hand. As already pointed out by previous research,[17] the functional impact of this treatment needs further clarification. It has been suggested that any improvement in script is important while treating writer's cramp with BTX, but impossible to quantify objectively.[18] On the other hand, most of the patients' reports lack objective or quantifiable response variable.[19]

In our study, there was only one patient with improved score in AHF under placebo and three under the active substance. The patients themselves, however, reported a benefit after BTX application. This benefit was objectively observable when comparing the patients' performance of hand function subtests using video assessment. These changes only influenced the quality of performance on some subtests, but did not influence the final AHF score. The patients themselves were able to express perceptions of their own hand function using the 0-5 self-assessment scale. Eight out of the ten patients expressed BTX benefit in this way. Hence, the scale appears to be practical and helpful in describing how patients perceive their response to the treatment. The scale also indicated a placebo effect as two patients reported some benefit under placebo.

Since some data indicate brain reorganisation following therapy with BTX, in the future it would be interesting to investigate whether structural changes in the brain take place after long-term therapy with BTX.

Conclusion

While there was no statistically significant improvement on the Assessment of Hand Function scale for the botulinum session, a more reliable difference in favour of treatment was found on the 0-5 self-assessment scale. We believe that the AHF test is not sufficiently sensitive or at least not superior to simpler global scales. Hence, we confirmed that measurement of focal disability does not entirely clarify functional changes after treatment with Botulinum Toxin.

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