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Botulinum neurotoxin treatment improves force regulation in writer's cramp

Kirsten E. Zeuner, MD¹, Arne Knutzen¹, Lucas Pedack¹, Mark Hallett, MD², Günther Deuschl, MD¹, and Jens Volkmann, MD^{1,3}

¹Department of Neurology, Kiel University, Germany

²Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

³ Department of Neurology, University of Würzburg, Germany

Abstract

Writer's cramp patients show poor force regulation during handwriting, but also in other experimental tasks requiring fine motor control. Botulinum neurotoxin (BoNT) treatment is clinically effective in a substantial portion of writer's cramp patients, but the full mechanism of action remains enigmatic. BoNT possibly influences α - and γ -motoneurons through chemodenervation not only of extra-, but also intrafusal muscle fibres and might thus influence muscle spindle afferents. Hence, BoNT weakens injected muscles, but may also modulate sensory aspects of force control. Ten patients and 18 controls pressed their index finger on a force sensor tracking two visual targets: The first target consisted of five plateaus with successively higher force levels and alternated with ascending ramps. In the second target condition the same successive plateaus were to be reached by abrupt jumps. The generated force displayed as a time dependant curve. Root mean square of the difference between target and produced force level was calculated for each plateau / ramp / jump. Patients were treated with BoNT at week 4 and measured at baseline, weeks 2, 4, 6 and 8. Disturbed force regulation in patients for the plateaus and the second jump at baseline resolved after BoNT treatment, and the root mean square of force deviation decreased for the ramps. Fine force control was within the 95 % confidence interval of the control group after treatment. In conclusion, force regulation was disturbed in patients and improved after BoNT treatment. This is not compatible with a simple muscle weakening and might thus reflect improved sensorimotor integration.

Keywords

Focal hand dystonia; writer's cramp; force control; botulinum neurotoxin treatment; spindle afferents

Corresponding Author: Kirsten Zeuner, MD Department of Neurology Kiel University Neurozentrum Arnold Heller Strasse 3, Haus 41 24105 Kiel Germany Phone: +49-431-597-8501 Fax: +49-431-597-8502 k.zeuner@neurologie.uni-kiel.de.

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Introduction

Writer's cramp is characterized by co-contraction of antagonist muscles hand while writing [1]. This condition may result in part from a sensory disorder [2, 3], and patients have difficulties interpreting sensory input that occurs before and during movement [4]. They are less capable to regulate force properly indicating an impaired capacity to integrate sensory information into motor programming [5]. Moreover, they have difficulties to rapidly turn on and to voluntarily relax isometric force output of the wrist [6]. Writing pressure [7] and grip force on the writing pen are increased [8].

It is not clear, what type of receptors are involved. Slow type II receptors may not be responsible for impaired grip force control [9]. In contrast, fast adapting type II receptors are possibly involved in excessive grip force output [5]. Increased grip force during precision grip in the symptomatic hand was further enhanced by 100 Hz vibration, which is predominantly activated by Ia spindle afferents [10]. Vibration of the dystonic limb at rest induced dystonic co-contractions of the involved muscles [11, 12]. Patients showed an abnormal perception of induced motion by the tonic vibration reflex, but not of position [13, 14]. Thus, central processing of proprioceptive, kinetic information from Ia muscle spindles seem to be misinterpreted.

The standard treatment involves the injection of botulinum neurotoxin (BoNT) into the dystonic muscles. Selective chemodenervation weakens the muscles, which may alleviate dystonic spasms, but several observations support an additional effect on muscle spindle afferents [15, 16]. Often patients report the re-occurrence of symptoms although clinically dystonic movements cannot be seen, and the doses injected with the degree of weakness do not correlate with the efficacy of the treatment [15]. Hence, several investigators have proposed that BoNT may aid in sensory remodelling (e.g. by altering the threshold of muscle spindles) in patients with focal dystonia [15, 17-19].

Fine force control is a prerequisite of coordinated handwriting and depends more prominently on reafferent control than on muscle strength. Therefore, the aim was to investigate differences of force regulation between writer's cramp patients and controls. We hypothesized that disturbed force control in writer's cramp patients would improve after BoNT treatment. For this purpose we developed an apparatus to measure the isometric force generated in the metacarpophalangeal joint of the right index finger in two different tasks. The index finger of the right dominant hand was chosen, because it is especially important for handwriting.

Methods

Patients and Controls

Ten patients with writer's cramp (7 females) volunteered for three pre-BoNT (weeks 0, 2, 4) and two post- BoNT evaluations (weeks 6 and 8). Mean age was 57.1 ± 10.7 years (range: 40-69 years), patients characteristics are given in table S1. The diagnosis was established by medical history and standard neurological examination including a writing test. 18 age-

matched healthy individuals served as controls (9 females). Mean age was 57.0 ± 9.1 years (range: 42-71 years).

Study Design

All five visits consisted of force control recordings and clinical assessments with the Arm Dystonia Disability Scale (ADDS) [20] and the Writer's Cramp Rating Scale (WCRS) [21]. The baseline measurement was conducted at least three months after any BoNT treatment (table S1). The visits were carried out in intervals of two weeks (week 0 / baseline, weeks 2, 4, 6 and 8). At week 4 BoNT (Dysport™, Ipsen, dilution 500 mouse units/2.5 mL 0.9 % saline solution) was injected under electromyographic guidance according to an individual injection pattern. The majority of patients were injected in the radial and / or ulnar part of the wrist flexors and / or the superficial and deep finger flexors with a range between 20 and 160 MU per patient (table S1). All participants gave written informed consent before the study. The study was conducted in full accordance to the Declaration of Helsinki and had been approved by the local ethics committee in Kiel.

Force Tracking Recordings

The apparatus (figure S1) was built by the Institute of Physiology of Kiel University. A force sensor (FORT 1000, World Precision Instruments, Sarasota, FL, USA) was connected with an amplifier (gain 1000, offset adjusted between -5 and $+5$ V) and to a CED Power 1401 (Cambridge Electronic Design (CED), Cambridge, Great Britain). Amplified data were fed into a personal computer that displayed the applied force as a time dependant curve. Signal Software 4.02 (CED) was used for the recordings and analyses of the traces. The forearm, wrist and hand were fastened in a splint with the fingers free to move. A clamp fixed the force sensor and immobilized the proximal and distal interphalangeal joints. Therefore the force was generated only by the metacarpo-phalangeal joint of the index finger.

The force sensor recorded at maximum 500 g (4.90 N). All patients were able to generate 4.9 N before and after BoNT treatment. The software program calculated the different force levels (0 N, 0.98 N, 1.96 N, 2.94 N, 3.92 N). All individuals pressed the index finger on the force sensor according to a visual line shown on a thin film transistor (TFT) display (14", 1m distance). Two different traces were presented to the subject: The first target included five horizontal plateaus indicating the different force levels separated by ascending ramps (figure 1 A). The duration of each ramp and each plateau was 5 sec. The second target consisted of plateaus with jumps between each force level. Each plateau lasted 10 sec. Feedback about the produced force level was provided by a superimposed cursor trace on the screen. To get accustomed, each target started with a 5 sec pre-trial time, which was excluded from the analysis (Figure 1A). The two different targets were presented in randomised order to each subject five times. The first run was always rejected, the remaining four runs analysed. In figure 1B examples for both tasks of control subject 16 are shown. In summary, we investigated the ability to accurately control force to match it to a visual stimulus during an isometric finger flexion.

Analysis

We calculated the difference between target and produced force levels over time with Signal Software 4.02 (CED). The root mean square of force deviations of each plateau / ramp / jumps was used for further statistical analysis. In the first target the points of change between plateaus and ramps were set after 5 sec and analysed separately. In the second target the cut off for the plateau was determined after 1 sec of the beginning of the plateau and 0.5 sec before the plateau ended. Since each plateau in the second target was recorded for 10 sec, 8.5 sec were included for the analysis of the plateau. The jumps started 0.5 sec before the end of the plateau and lasted 1 sec into the next, successive plateau. Therefore each jump lasted 1.5 sec (Figure 1).

Clinical Assessment

Patients were videotaped during writing the sentence “Die Wellen schlagen hoch” (“The waves are surging high”) ten times without a break between consecutive sentences. A neurologist (K.E.Z.) unaware of the treatment status assessed symptom severity from the video segments (face not shown) using the WCRS [21]. The higher the total WCRS score the more severe are the dystonic symptoms during handwriting [21].

The ADDS contains seven items which estimates the impairment of manual skills reported by patients. A score of 100 % indicates normal motor function. The final score presents the percentage of normal manual activity. Accordingly, the lower the ADDS score the more severe is the functional impairment [20].

Statistical Analysis

Statistical Analysis—The root mean squares of force deviation were assessed as dependent variables in separate analyses (SPSS statistics 19) as follows: The mean of the first three measurements (weeks 0, 2 and 4) before the BoNT injection served as baseline in the patient group. In the first analysis, patients were compared to controls using the unpaired t-test. Each target and task required different aspects of force control and was analyzed separately: Target 1: task 1 horizontal plateaus (HP 1 - 5) alternated with task 2, the ascending ramps (AR 1 - 4); target 2: task 1 steps plateaus (SP 1 - 5) alternated with task 2, the jumps (C 1 - 4). A separate two-factorial ANOVA was computed in the patient group for each of the targets and tasks: *time of measurement* (baseline, weeks 6 and 8) and *horizontal plateau* (HP 1 – HP 5) as within-subject factor; *time* and *ascending ramps* (AR 1 - 4); *time* and *steps plateau* (SP 1 - 5) and *jumps* (C 1 - 4). In controls the two- factorial ANOVA was applied and included baseline and week 4 as *time of measurement*. The effect of BoNT treatment on the clinical scores was evaluated by one-factorial ANOVAs using *time* (baseline, weeks 6 and 8) as within-subject factor. If necessary, Huynh-Feldt method was used to correct for non-sphericity. Conditional on the respective significant *F* value, post-hoc paired (within-subject factor) or independent (between-subject factor) t-tests were used to explore the direction of main effects or the patterns of interaction between factors. Further, the relation between changes of horizontal plateaus or ascending ramps, the doses of BoNT, WCRS and ADDS were evaluated with the Spearman correlation for each parameter in the patient group. A p-value of 0.05 or less was considered significant. The results are reported as mean $\pm$ SD.

Results

Clinical Results

The mean WCRS score for the ten patients was 10.37 ± 5.68 at baseline and 8.90 ± 7.13 four weeks after treatment (week 8), while the ADDS changed from 57.6 ± 22.7 to 55.86 ± 27.1 (table S1). ANOVA showed no time effect in either clinical score. All patients noted weakness of the injected muscles after the BoNT treatment.

Root mean square of force deviation for task one in target one: Horizontal Plateaus

Force regulation differed between patients and controls at baseline for the first plateau: $T(26) = -2.28$; $p = 0.031$ and a trend for the second plateau: $T(26) = -1.96$; $p = 0.06$ (Figure 2A). These differences dissolved after the BoNT treatment (weeks 6 and 8). The two-factorial ANOVA revealed no main effect in patients for *horizontal plateau* or interaction between *horizontal plateau*time of measurement*, but a trend for *time of measurement* ($F_{2,0;18} = 2.84$; $p = 0.084$) suggesting that BoNT might have an effect on force control. To further identify the time points at which the improvement of force control occurred, the mean of all horizontal plateaus was calculated and the paired t-test applied. The root mean square of force deviation descended between baseline and week 8 ($T(9) = 2.89$; $p = 0.018$). The BoNT effect occurred on all horizontal plateaus (HP 1 to 5) (Figure 3 A). Between baseline and week 6 an additional improvement for HP 3 was detected (for details see table 1). The results of all patients after treatment stabilized within the 95 % confidence interval of the controls. In healthy subjects, the root mean square of force deviation remained the same for all plateaus between weeks 0 and 4 (figure S2 A). While improved force regulation showed no correlation with clinical scales, higher BoNT doses correlated with increased improvement for the second ($p=0.017$) and fifth ($p = 0.025$) plateau, with this single factor explaining 24 % (51 %) of the variance.

Root mean square of force deviation for task two in target one: Ascending Ramps

Force regulation was not impaired in patients compared to controls in ramps. The three-factorial ANOVA revealed a main effects of *time of measurement* ($F_{1,81;16.3} = 4.33$; $p = 0.029$), but no additional main effect for *ramp* or *ramp*time interaction* emerged. BoNT lead to a decrease of the root mean square of force deviation four weeks after the injection ($T(9) = 2.68$; $p = 0.025$), mainly in ramps 2 and 4 (table 1). There was no association between the ramp changes and the BoNT dose or clinical parameters. In controls force control in ramps remained unchanged between weeks 0 and 4.

Root mean square of force deviation for task one in target two: Steps Plateaus

Controls and patients differed in SP 2 to 5 (SP 2 ($T(26) = -3.07$; $p = 0.005$), SP 3 ($T(26) = -2.98$; $p = 0.006$), SP 4 ($T(26) = -2.88$; $p = 0.008$) and SP 5 ($T(26) = -2.10$; $p = 0.046$) (Figure 2 B). After BoNT treatment, fine force control in patients stayed within the 95 % confidence interval of the control group. Healthy subjects showed no differences between weeks 0 and 4 (figure S2 B).

Comparable to the effect of BoNT in HP, the two factorial ANOVA revealed a main effect for *time* ($F_{1,16;10.5} = 5.42$; $p = 0.037$), but not for *steps plateau* or *steps plateau*time*

interaction. Post hoc analysis using the mean for SP1 to SP5 displayed the improvement four weeks after the injection ($T(9) = 2.66$; $p = 0.026$), which occurred for SP 2, SP 3 and SP 5 (Figure 3 B). There was no correlation between the clinical parameters or BoNT doses and improvement in steps plateau.

Root mean square of force deviation for task two in target two: Jumps

Differences between controls and patients occurred only for the second jump ($T(26) = -2.34$; $p = 0.027$). Force control remained stable in controls, and BoNT had no effect on jumps in patients and there were no correlations between a benefit in dystonic symptoms and force control.

Discussion

In summary, the ability to accurately control and match force to a visual stimulus was disturbed in writer's cramp patients particularly for steady force levels, whereas slow or rapid force adjustments were comparable to normal subjects. BoNT treatment corrected these deficits to levels within the 95 % confidence interval of healthy subjects. Improvement in clinical parameters and force regulation were not correlated. In the first task of target one, force control was impaired especially for lower strength, but improved for all force levels after BoNT treatment. In the second target, task 1 patients had difficulties in maintaining the force of the next plateaus after abrupt jumps, while they were able to adjust their force for higher levels with slowly increasing force as in task 1 of target 1. The plateau phases in the second target lasted 8.5 sec compared to 5 sec in the first target. Presumably, it was more difficult for patients to hold a longer plateau level for lower and higher strength. The force sensor recorded the maximum force of 500 g (4.90 N), and all patients were able to generate this force throughout the measurements. Therefore it is unlikely that the maximal strength of writer's cramp patients before and after the BoNT treatment and controls contributed to the change of force regulation.

Former studies demonstrated that feedback of tactile information is relevant to control grip force. The signals in afferents coming from the fingers play an important role in precision of motor control, and anaesthesia of the finger abolished the capacity to adjust the grip force [9], especially when only digital movements are allowed as it is the case in our study [22]. Tactile input might also be responsible for the initiation and the scaling of the grip response [23]. Accordingly, afferent input is crucial especially for precise force control. Since it is evident that focal hand dystonia is a disorder of perception and sensory integration [3, 24], disturbed fine force control in our study might account for disturbed sensory integration.

In writer's cramp patients, minimal force (HP 1) control was affected in the first task. This finding confirms the clinical observation that predominantly high precision movement at low force exertion is impaired [24]. The precision grip, which has predominantly been used to measure force control, has similarities with our force tracking task. It is confined to the tips of the index finger and thumb and involves smaller forces. Patients with writer's cramp displayed not only an increase in grip force [10] particularly during the static phase, but showed an additional sequential initiation of grip and load force at the beginning of the loading phase [5]. These findings suggested that sensory afferents to central structures are

disturbed. It has been postulated that fast adapting type II receptors (FA II) contributed to force adjustment during the static phase of the lift.

Several different other receptors beside FAII receptors were involved during our measurements. Force was generated by the metacarpophalangeal joint, and subjects pressed the index finger on the force sensor. Presumably, pressing the index finger on the force transducer stimulated slow adapting type I receptors (SA I) [5]. However, we did not perform measurements under local anaesthesia of the index finger to exclude tactile afferent information through mechanoreceptors as a control experiment. On the other hand, BoNT improved force control in our study; hence it is unlikely that only mechanoreceptors were involved.

In our study it was more difficult for patients to hold longer plateau levels compared to jumps. In such a setting more spindle Ia afferents are activated due to the co-activation of α - and γ -motoneurons (α - and γ -coupling) [25]. This could imply that in patients with dystonia diminished perception of Ia afferents accounts for the impairment to control isometric force. The α - γ co-activation is required for the “servo control” of muscle length and tension [26]. It is conceivable that dystonia has an impact on α - γ -co-activation due to an abnormal activation of the intrafusal muscle fibres [26].

It was recently shown in controls, that vibration of the masseter muscle causes an illusion of jaw opening, which reflects the response of spindle Ia and II afferents [25]. In patients with writer's cramp, the tonic vibration reflex (TVR) measuring the activity of spindle Ia afferences, was depressed after BoNT treatment, a finding that was interpreted to reflect the effect of the toxin on the innervation of the intrafusal fibers [19]. Recently, it has been discussed that spindle Ia/II afferents are also involved in the execution of isometric contractions by activating γ -motoneurons [25], and the improvement of force control after treatment in our study might thus result from normalizing sensory control and α - γ -co-activation. However, we did not measure the effect of BoNT on the intrafusal and extrafusal muscles directly and it remains a hypothesis that the improvement of force control was caused by a chemodenervation of extrafusal and intrafusal muscles. Because BoNT diffuses into adjacent muscles, it is a reasonable assumption that spindle afferents of both, the neighboring wrist and finger flexor muscles could have been affected by an injection into either one of these.

The antidystonic effect of BoNT is probably caused not only by weakening the injected muscles, but also by increasing spinal reflex inhibition [26]. Supposedly, BoNT might restore abnormal activation of the intrafusal muscles fibres and improve disturbed sensorimotor integration through two different tracks: First, through afferent pathways at the injected site that cause reorganization in the central nervous system; Second, the paresis might cause altered motor and sensory perception and finally also a reshaping in the central sensorimotor system.

Since significant associations between the doses in Mouse Units of BoNT injected explained only 24 % (HP 1) and 51 % (HP 5) of the variance, we assume that the number of muscles injected is more important than the doses applied as suggested in earlier studies [15].

Possibly, lower injection doses in more locations could influence more spindle afferents, result in a better outcome and prevent involuntary weakness and result in a better functional outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A: Timing of the force tracking tasks with the two different tasks presented to each subject *Target 1*: horizontal plateaus alternated with ramps; each plateau/ramp lasted for 5 sec with a pre-trial-time of 5 sec and a total time length of 50 sec; plateaus (P1-P5) and ramps (r1-r4) were analyzed separately.

Target 2: horizontal plateaus varied with jumps; separate analysis of plateaus (p1-p5) and jumps (c1-c4); total length of 55 sec included a 5 sec pre-trial-time; each plateau lasted 10 sec; the jumps started 0.5 sec before the end of the plateau and lasted 1 sec into the next, successive plateau. Therefore each jump lasted 1.5 sec, the plateau phase for evaluation 8.5 sec.

B: An example of a normal volunteer (K16) is demonstrated here. In the first task the points of change between plateaus and ramps were set after 5 sec and analysed separately. In the second task the cut off for the plateau was determined after 1 sec of the beginning of the plateau and 0.5 sec before the plateau ended. The default line was subtracted from the traces that were recorded in each task. The root mean squares of each plateau/ ramp/ jumps were calculated. The result was the root mean square of force deviation.

Figure 2.

A. Results for the first target for the horizontal plateau (HP) 1 to 5 in controls and patients at baseline are demonstrated. Baseline in patients consisted of the mean of the first three measurements (weeks 0, 2 and 4). The root mean square of force deviation was increased in patients in HP 1 and a trend could be seen for HP 2 ($p=0.06$). Light columns = controls (C), dark grey columns = patients (P). Error bars equal onefold standard error of the mean; asterisks indicate a p-value of <0.05 .

B. Results for steps plateaus (SP) 1 to 5. The root mean square of force deviation was increased in patients in SP 2, 3, 4. Error bars equal onefold standard error of the mean; asterisks indicate a p-value of <0.05 . C = controls, P = patients

Figure 3.

A. Results of horizontal plateaus (HP 1 to 5) at baseline and weeks 6 and 8 in patients. Improvement of force regulation occurred for HP 1 to 5 between week 0* and week 8. Light grey columns = week 0* (week 0* = baseline = mean of the first three measurements (weeks 0, 2 and 4). BoNT was injected at week 4. Dark grey = week 6 and black columns = week 8.

B. Results of steps plateau (SP 1 to 5) at week 0*(baseline) and after the BoNT treatment at weeks 6 and 8. Improvement of force regulation occurred for SP 2, 3, 5 between baseline and week 8.

Asterisks indicate a p-value < 0.05. Error bars equal onefold standard error of the mean.

Table 1

Results of post hoc T-test for each target in patients with writer's cramp

Target	Significant change Between baseline to wk 6	Significant change Between baseline to wk 8	Post hoc t-value Baseline to wk 8	Post hoc p-value Baseline to wk 8
HP 1		x	T(9) = 2.58	p = 0.03
HP 2		x	T(9) = 3.21	p = 0.01
HP 3	x	x	T(9) = 2.44	p = 0.04
HP 4		x	T(9) = 2.30	p = 0.03
HP 5		x	T(9) = 2.57	p = 0.03
AR 1		x	T(9) = 2.25	p = 0.05
AR 2		x	T(9) = 2.60	p = 0.03
AR 3		x	T(9) = 2.20	p = 0.06
AR 4		x	T(9) = 2.52	p = 0.03
SP 1			n.s.	n.s.
SP 2	x	x	T(9) = 2.70	p = 0.02
SP 3	x	x	T(9) = 2.34	p = 0.04
SP 4			n.s.	n.s.
SP 5	x	x	T(9) = 2.81	p = 0.02
AC 1			n.s.	n.s.
AC 2			n.s.	n.s.
AC 3			n.s.	n.s.
AC 4			n.s.	n.s.

Legend: HP = horizontal plateau; AR = ascending ramps; SP = Steps Plateau; AC = jumps; n.s. = not significant; wk = week. The mean of the first three measurements (weeks 0, 2 and 4) before the BoNT injection served as baseline in the patient group.