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ORIGINAL RESEARCH

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The effect of botulinum toxin-A on neural and non-neural components of wrist hyper-resistance in adults with stroke or cerebral palsy

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Abstract

Background: Botulinum toxin-A (BoNT) is widely used to manage focal upper limb spasticity and is effective in reducing resistance to passive movement, as measured with the modified Ashworth scale. Discrimination and quantification of the underlying neural and non-neural components of hyper-resistance may further improve understanding of the effect of BoNT.

Objective: To explore the effects of BoNT on neural (NC), non-neural elastic (EC), and viscous (VC) components of resistance to passive wrist extension in adults with stroke or cerebral palsy and the association between the effects on wrist hyper-resistance components and clinical spasticity, pain and motor function scales.

Design: Pre-experimental study with pre- and post-intervention measurements at 6 and 12 weeks.

Setting: An outpatient clinic of a hospital.

Participants: Adults with chronic stroke or cerebral palsy indicated for BoNT treatment for hyper-resistance in the wrist (N = 18).

Interventions: BoNT injections in the wrist and/or finger flexor muscles.

Main Outcome Measures: Wrist hyper-resistance components, using the NeuroFlexor, and clinical scales (modified Ashworth scale, Tardieu scale, passive wrist extension, pain, Fugl-Meyer motor assessment of the upper extremity, and action research arm test).

Results: NC was significantly reduced 6 and 12 weeks post-intervention (median −11.96 Newton, $P < .001$ and median −9.34 Newton, $P = .001$, respectively); non-neural EC and VC showed no change. NC reduction 6 weeks post-intervention correlated significantly with BoNT dose (Pearson correlation coefficient $r_p = -0.56$). No significant correlations were found between change scores in wrist hyper-resistance components and clinical scales.

Conclusions: BoNT affected the neural component of resistance to passive wrist extension, while leaving the non-neural elastic and viscous components unaffected. This instrumented approach to quantify the effects of BoNT in the wrist and finger flexor muscles on the components of wrist hyper-resistance may have an added value for BoNT treatment evaluation in clinical practice.

INTRODUCTION

Botulinum toxin-A (BoNT) therapy is the treatment of choice for focal upper limb spasticity. BoNT causes a temporary reduction of muscle activity by blocking the release of acetylcholine at the neuromuscular junction.[1] A recent systematic review[2] has shown robust evidence for the effectiveness of BoNT treatment for upper limb spasticity after stroke in reducing resistance to passive movement at the International Classification of Functioning, Disability and Health (ICF) level[3] of body functions, measured with the modified Ashworth scale (MAS), and improving self-care ability of the affected limb at the ICF activities level. A favorable effect of BoNT treatment on other body functions is suggested in reducing spasticity-related pain and involuntary movements, and improving passive range of motion, whereas no effects were found regarding improvement of arm and hand use, at both body functions and activities levels. The underlying mechanisms and evidence for the generalizability of effectiveness of BoNT in the upper limb need further underpinning.[4-6]

Since the 1990s,[7] many studies question the validity of the MAS as an adequate measure for the evaluation of spasticity and more specifically BoNT treatment on an individual level.[2] The ordinal scaled MAS provides only a subjective estimate of the total perceived resistance to passive movement whereas increased resistance, that is, hyper-resistance, is hypothesized to be caused by a complex interaction between pathological neuromuscular activation, including spasticity[8] and involuntary baseline activation,[9] and altered viscoelastic tissue properties of the muscles spanning the joint.[10,11] Moreover, the contribution of aforementioned neural and non-neural tissue components might vary between individual patients with upper limb hyper-resistance[12] and may change over time.[13-15] BoNT treatment is expected to primarily affect the neural component. This latter assumption suggests that the cost-effectiveness of this expensive BoNT treatment may be improved by a better selection of patients, dependent on which component dominates. Aforementioned problems in BoNT treatment indication and evaluation may be overcome by using instrumented measurement techniques that can discriminate between neural and non-neural components of hyper-resistance and that are clinically applicable.

The commercially available NeuroFlexor (Aggero MedTech AB, Ita, Sweden) is developed to quantify neural (NC), non-neural elastic (EC), and viscous (VC) components of hyper-resistance in the wrist and finger flexor muscles in clinical practice. This measurement technique was shown to be valid,[16,17] reliable,[17,18] and responsive to change.[15] In a first study[19] it was shown that the NC, as measured with the NeuroFlexor, was responsive to monitor mean change after BoNT treatment in patients post stroke.

The aim of the present pre-experimental study was to explore (1) the effects of BoNT treatment in the wrist and/or finger flexor muscles on the NC, EC, and VC of resistance to passive wrist extension measured by the NeuroFlexor in adults with stroke or cerebral palsy (CP), and (2) the association between the effects on wrist hyper-resistance components and recommended clinical scales at the ICF level of body functions, that is, MAS, Tardieu scale (TS), passive wrist extension, numeric rating scale for self-reporting of pain, and Fugl-Meyer motor assessment of the upper extremity (FM-UE), and at the level of activities, that is, action research arm test (ARAT).

METHODS

Patients

All patients scheduled for BoNT treatment between January 2018 and June 2019 at the outpatient rehabilitation department of a teaching hospital (Spaarne Gasthuis, Hoofddorp, The Netherlands) were screened for eligibility. Inclusion criteria were (1) patients greater than 3 months post stroke or with a diagnosis of CP, (2) clinically appropriate for botulinum toxin-A treatment in the wrist and/or finger flexor muscles by an experienced rehabilitation physician, (3) at least 18 years old, and (4) able to understand test instructions. Exclusion criteria were (1) less than 0° passive wrist extension with extended fingers, and (2) other medical disorders, such as osteoarthritis, influencing wrist hyper-resistance. The need for medical ethical certification was waived by the Medical Ethics Committee of the Vrije Universiteit medical centre, Amsterdam, The Netherlands (2017.440) as this study was performed within the context of usual care. In accordance with the Declaration of Helsinki, all participating patients gave written informed consent.

Study design and BoNT treatment

In this prospective clinical cohort study with longitudinal measurements, patients were examined on three occasions: pre-intervention (in the hour before BoNT treatment) and at 6 and 12 weeks post-intervention. All measurements were performed by a trained physiotherapist or occupational therapist, who was unaware of the BoNT treatment dose.

All patients received intramuscular onabotulinum toxin-A injections (Botox, Allergan, Irvine, CA, USA) with the exception of one patient who received incobotulinum toxin-A (Xeomin, Merz Pharmaceuticals GmbH, Frankfurt, Germany) in one or more wrist and/or finger flexor muscles. All injections were performed under ultrasound guidance by the same physician (W.P.). Injected muscles, dosage, and injection sides of the BoNT were individualized for each patient based on the patient's clinical presentation and treatment goals, the physician's clinical experience, and on the national guideline for cerebral

and/or spinal spasticity of the Federation of Medical Specialists. Results of the NeuroFlexor measurements were not presented to the physician during the study to avoid influence on the individual treatment plan. No additional therapy was prescribed outside usual care.

Outcome measures

Neural and non-neural components of wrist hyper-resistance

The NeuroFlexor, as shown in Figure 1, applies isokinetic positional perturbations to the wrist with extended fingers from 20° flexion toward 30° extension at two controlled velocities (5 and 236°/s). When passive wrist extension was less than 40°, the perturbation range was adjusted to a 50° range ending 10° before maximal extension. Total resistance during wrist extension was measured in Newton (N) using a force sensor mounted underneath the moveable hand platform. The patient was seated comfortably parallel to the NeuroFlexor with the shoulder in 45° abduction, 0° flexion, the elbow in 90° flexion and the forearm in pronation fixated to the device. The hand was Velcro-strapped onto the hand platform. The wrist joint was visually aligned to the rotation axis of the device. A measurement session consisted of five slow followed by 10 fast movements. The first movement at both velocities was excluded from analysis to avoid bias from startle reflexes and mechanical hysteresis. A biomechanical, unidirectional wrist model[16] using a force-relationship method based on the mean resistance trace of the slow and the fast movements, was applied to calculate the components of wrist hyper-resistance, that is, NC, EC, and VC, directly after each measurement (software program NeuroFlexor Scientific v0.06, Supplementary Appendix S1). Resting force (RF) is the force of the hand on the hand platform before onset of stretch, with wrist angle equals 20° flexion, as depicted as P0 in Figure 1 (B),(C).

Clinical assessments

Total resistance to passive wrist extension was measured for wrist and finger flexor muscles using the MAS,[20] an ordinal scale with scores ranging from 0, no increased tone, to 4, total joint rigidity. Wrist movement with flexed fingers was regarded representative of resistance mostly caused by the wrist flexor muscles, wrist movement with extended fingers as representative of resistance mostly caused by the finger flexor muscles. The TS[21] was used to assess passive wrist extension at one slow velocity (R2, "as slow as

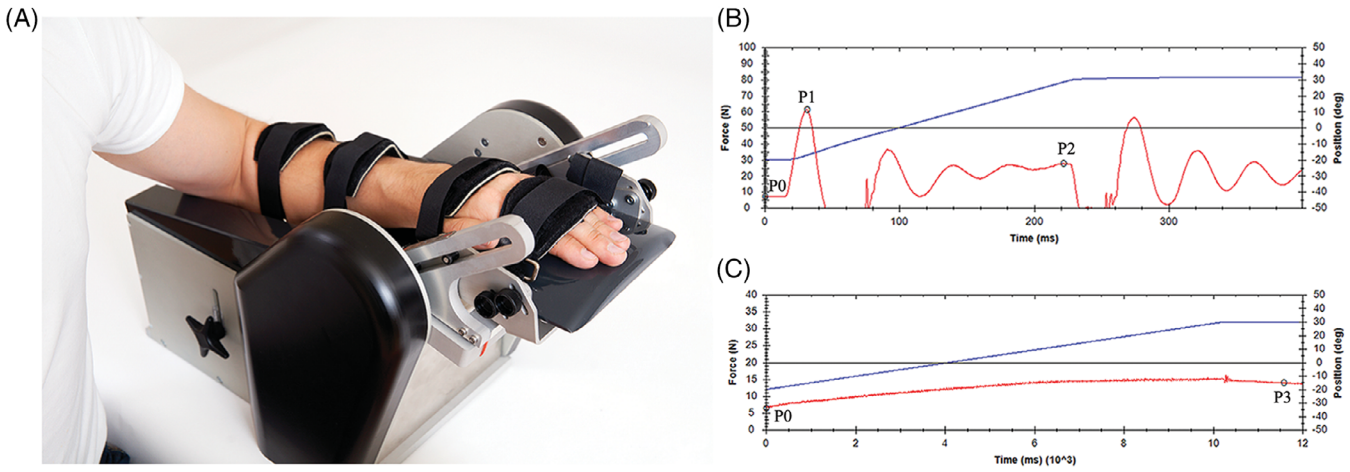

FIGURE 1 NeuroFlexor method. (A) Measurement setup. (B–C) An example of the force traces (red line) from a patient (NC: 13.91 N, EC: 6.03 N, RF: 6.64 N, MAS: 1+) obtained during (B) a fast passive wrist extension movement (236°/s) and (C) a slow passive wrist extension movement (5°/s). The blue line represents the angle of the wrist joint. The recorded force traces, measured in Newton (N), are analyzed by a biomechanical model, which results in the quantification of the neural component (NC), elastic component (EC), and viscous component (VC) of wrist hyper-resistance. The total measured resisting force (F_m) during passive wrist extension is a summation of passive elastic force (F_p), viscous force (F_v), reflexive force (F_r), and inertial forces of the limb and the moving parts of the device (F_{in}), described as: $F_m(\theta) = F_p(\theta) + F_v(\theta) + F_r(\theta) + F_{in}(\theta)$, where θ denotes a specific angle. In the model, four force magnitudes, identified in the force-time-traces of the slow and fast movements, are used to estimate the different components of the total measured passive force. P0 is the resting force of the hand before onset of stretch, with wrist angle equals 20° flexion. Two force magnitudes are defined within the fast passive wrist extension movement (236°/s): P1, the initial force peak, and P2, the late force peak (at the end of the movement). One force magnitude (P3) is defined at the end position of the slow wrist extension movement (5°/s). Resting force (P0) is subtracted from P1, P2, and P3 prior to further calculations. Detailed information about the biomechanical model can be found in Supplementary Appendix S1. Abbreviations: MAS, modified Ashworth scale; RF, resting force

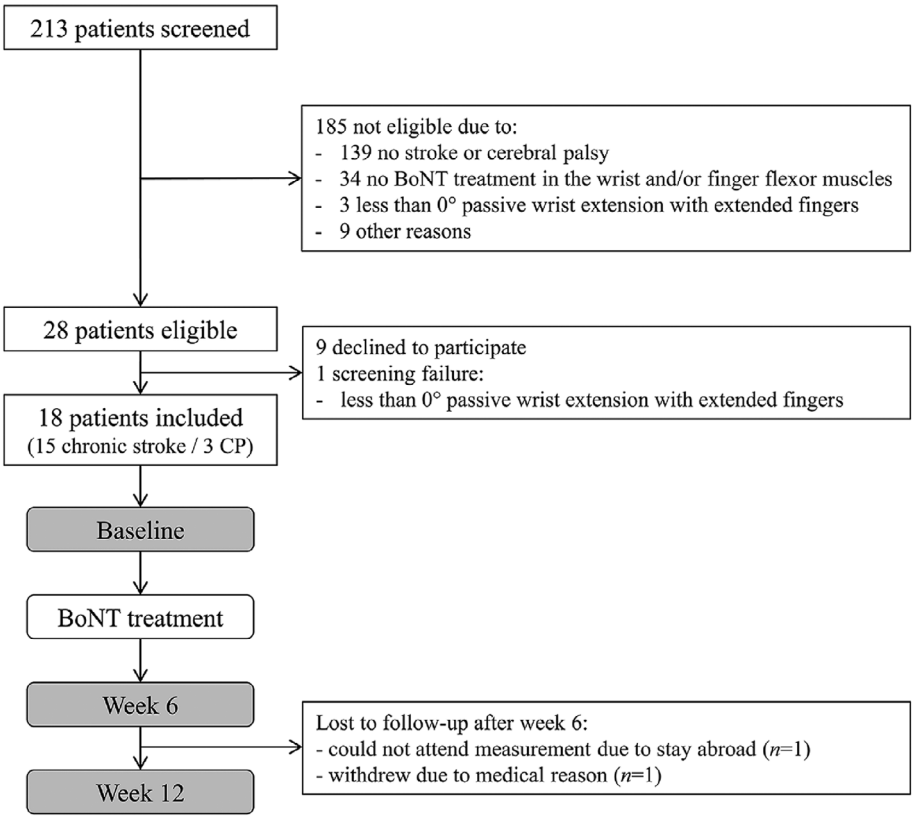

FIGURE 2 Flow chart

possible"), joint angle of muscle reaction at one fast velocity stretch (R1, "as fast as possible"), and quality of muscle response at fast speed. Passive wrist extension angle at fast velocity (R1) subtracted from passive wrist extension at slow velocity (R2) represents the velocity-dependent resistance element ($TS_{R2\text{-}R1}$). Quality of the muscle response at fast speed (TS_Q) is described on an ordinal five-point scale, where 0 means no resistance to passive movement, and 4 means a clonus that does not cease within 10s. Passive wrist extension with fingers flexed and extended was assessed using goniometry at a constant torque of 2 Nm applied at the hand palm controlled by a hand-held dynamometer. Pain in the upper limb was assessed by a numeric rating scale (range 0–10). The FM-UE[22] was used to assess motor performance of the affected arm and hand with a scoring range from 0 to 66 points. The ARAT[23] was used to assess arm and hand capacity with a scoring range from 0 to 57 points. Both the FM-UE[24] and ARAT[23] are valid and reliable tests in stroke patients.

Statistical analysis

Study data were analyzed using SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for demographic and clinical characteristics. For all variables, normality was assessed by inspecting histograms and Q-Q plots. A Shapiro-Wilks test was carried out on all outcome variables on the three different time points. The majority of data was non-normally distributed. Differences between the measurements over time for the wrist hyper-resistance components and the clinical scales were calculated using Friedman one-way repeated measures analysis. Post hoc Wilcoxon signed-ranks tests with Bonferroni correction were used to identify where the statistical differences occurred between the three time points. Correlation coefficients between change of wrist hyper-resistance components and the ratio scaled clinical scales, as well as the correlation coefficients with the injected BoNT dose were calculated using Pearson Product Moment correlation coefficients (r_p). Spearman's rank correlation coefficients (r_s) were calculated to assess the relationship between change of wrist hyper-resistance components and the change scores of the ordinal scaled clinical scales. Correlation coefficients below 0.20 were classified as very weak, between 0.20 and 0.39 as weak, between 0.40 and 0.59 as moderate, between 0.60 and 0.79 as strong, and above 0.80 as very strong.[25] The level of significance was set at .05.

RESULTS

A total of 213 patients scheduled for BoNT treatment were screened for eligibility, and 19 patients were

TABLE 1 Demographic and clinical characteristics of the study population (n = 18)

Age, years	57.8 ± 13.3
Gender, male/female (*n*)	11/7
Diagnose, iCVA/hCVA/CP (*n*)	12/3/3
Time post stroke, years (*n* = 15)	7.2 ± 5.4
NIHSS score	4.6 ± 3.0
Affected side, left/right (*n*)	7/11
Previous BoNT treatments (*n*)	
0 treatments	2
1 to 5 treatments	1
6 to 10 treatments	8
More than 10 treatments	7
Wrist flexor muscles	
MAS	1.5 [1–2]
TS_Q	2 [1–2]
$TS_{R2\text{-}R1}$ (°)	50.7 ± 42.3
WE_{FF} (°)	57.7 ± 22.7
Finger flexor muscles	
MAS	1.5 [1–2]
TS_Q	2 [1–2]
$TS_{R2\text{-}R1}$ (°)	43.0 ± 42.5
WE_{FE} (°)	51.6 ± 23.1
FM-UE	14 [7–22]
ARAT	3 [0–6]

Note: Values are mean ± SD or median [25th–75th percentile].
Abbreviations: ARAT, action research arm test [range 0–57]; BoNT, botulinum toxin-A; CP, cerebral palsy; FM-UE, Fugl-Meyer motor assessment of the upper extremity [range: 0–66]; hCVA, hemorrhagic stroke; iCVA, ischemic stroke; MAS, modified Ashworth scale [range 0–4], (score 1+ is reported as 1.5); NIHSS, National Institutes of Health Stroke Scale [range: 0–42]; TS_Q, Tardieu scale, quality score; $TS_{R2\text{-}R1}$, Tardieu scale, passive wrist extension angle at slow velocity (R2) minus passive wrist extension angle at fast velocity (R1); WE_{FE}, passive wrist extension, fingers extended; WE_{FF}, passive wrist extension, fingers flexed.

TABLE 2 Botulinum toxin-A treatment

Muscle	Patients injected (*n*)	Dose, unit (median)
m. flexor digitorum superficialis	16	75
m. flexor digitorum profundus	16	75
m. flexor carpi radialis	10	75
m. flexor carpi ulnaris	8	50
m. lumbricalis	10	50
m. palmaris longus	6	25
m. flexor pollicis longus	9	50
m. flexor pollicis brevis	7	25
m. opponens pollicis	7	25
m. extensor carpi radialis	1	25
m. extensor carpi ulnaris	1	40
m. extensor digitorum	1	50
m. extensor pollicis brevis	1	25
m. abductor digiti minimi	1	25
m. pronator teres	8	50
m. pronator quadratus	1	25
m. brachialis	9	50
m. brachioradialis	3	50
m. biceps brachii	6	75
m. triceps brachii	2	37.5
m. pectoralis	3	100

Gray colored injected muscles affect wrist hyper-resistance, as measured by the NeuroFlexor.

included in the study. Of those 19 there were 16 patients with chronic stroke and three patients with CP (Figure 2). One patient with chronic stroke was excluded after the screening procedure as, in contrast to the primary clinical measure, passive wrist extension with fingers extended using goniometry at a constant torque of 2 Nm was less than 0°. Two patients were lost to follow-up after week 6. Table 1 presents an overview of the demographic and clinical characteristics of the study population pre-intervention. Patients received a mean total dose of 394 ± 176 units of BoNT (Botox or Xeomin), of which 288 ± 123 units in muscles affecting wrist and/or finger joints (Table 2 and Supplementary Appendix S2). Patients with chronic stroke received a higher dose of BoNT compared to patients with CP (total dose: 442 ± 151 vs 158 ± 52, and dose in muscles affecting wrist and/or finger joints: 323 ± 101 vs 108 ± 14 units). No serious adverse events related to the BoNT treatment were reported during the study. Post-intervention measurements were performed on average (±SD) 44 ± 5 days and 87 ± 7 days after treatment, respectively.

Table 3 shows the pre- and post-intervention scores for all outcome parameters. The individual and median scores for the NC, EC, and VC of wrist hyper-resistance over time can be found in Figure 3 and Supplementary Appendix S2. Friedman one-way repeated measures analysis for the three time points showed a significant difference in NC (χ^2 [2] = 16.625, $P < .001$), EC (χ^2 [2] = 6.125, $P = .047$), and in RF (χ^2 [2] = 14.625, $p = .001$). Post hoc analyses showed significant reductions of the NC and RF 6 weeks post-intervention (NC: $Z = -3.549$, $P < .001$; RF: $Z = -3.419$, $P = .001$), a significant increase of the NC between week 6 and week 12 ($Z = -2.844$, $P = .004$), and overall significant reductions of the NC and RF 12 weeks post-intervention (NC: $Z = -3.206$, $P = .001$; RF: $Z = -2.896$, $P = .004$). The median NC was 20.47 N pre-intervention, 8.51 N at 6 weeks post-intervention, and 11.13 N at 12 weeks post-intervention. The median RF was 8.84 N pre-intervention, 7.59 N at 6 weeks post-intervention, and 8.00 N at 12 weeks post-intervention. Wilcoxon signed-rank tests

TABLE 3 Pre- and post-intervention scores of neural and non-neural components of wrist hyper-resistance and clinical scales

	Pre-intervention week 0 (*n* = 18)	Post-intervention week 6 (*n* = 18)	Post-intervention week 12 (*n* = 16)	*P* value
NeuroFlexor				
NC	20.47 [10.29–33.00]	8.51 [3.40–15.04][a]	11.13 [6.21–21.68][a b]	<.001
EC	6.84 [4.11–14.97]	4.95 [3.29–10.26]	7.74 [4.34–10.11]	.047
VC	0.29 [0.10–0.53]	0.45 [0.02–0.68]	0.36 [–0.09–0.80]	.646
RF	8.84 [7.59–10.81]	7.59 [5.07–8.53][a]	8.00 [6.09–9.48][a]	.001
Wrist flexor muscles				
MAS	1.5 [1–2]	1 [0–1.5]	1.5 [1–2]	.003
TS_Q	2 [1–2]	1 [0–2]	2 [1–2]	.042
$TS_{R2\text{-}R1}$	54 [0–96]	0 [0–66]	4 [0–60]	.099
WE_{FF}	61 [38–76]	79 [61–90]	67 [54–80]	.129
Finger flexor muscles				
MAS	1.5 [1–2]	1 [0–1.5]	2 [1–2]	.058
TS_Q	2 [1–2]	2 [0–2]	2 [1–2]	.143
$TS_{R2\text{-}R1}$	42 [0–85]	10 [0–69]	50 [0–79]	.544
WE_{FE}	52 [37–71]	68 [54–86]	60 [48–76]	.040
Pain average	2 [0–5]	0 [0–4]	1 [0–5]	.710
Pain worst	4 [0–7]	0 [0–5]	2 [0–7]	.201
FM-UE	14 [7–22]	14 [7–21]	16 [8–23][b]	.006
ARAT	3 [0–6]	3 [2–15]	3 [1–9]	.862

Note: Values are median [25th–75th percentile].
Friedman's test *P* value and post hoc Wilcoxon signed ranks tests are reported.
[a]Indicates a significant difference compared to baseline ($P < .050/3$).
[b]Indicates a significant difference compared to week 6 ($P < .050/3$). Gray-filled boxes indicate significant values after Bonferroni correction.
Abbreviations: ARAT, action research arm test; EC, elastic component (N); FM-UE, Fugl-Meyer motor assessment of the upper extremity; MAS, modified Ashworth scale; NC, neural component (N); Pain, range 0-10; RF, resting force (N); TS_Q, Tardieu scale, quality score; $TS_{R2\text{-}R1}$, Tardieu scale, passive wrist extension angle at slow velocity (R2) minus passive wrist extension angle at fast velocity (R1) (°); VC, viscous component (N); WE_{FE}, passive wrist extension, fingers extended (°); WE_{FF}, passive wrist extension, fingers flexed (°).

did not yield any significant difference of the EC between the time points. No significant change over time was found for the VC. Patients with CP showed a similar effect of BoNT as patients with stroke.

For the clinical scales, significant differences between repeated measurements were found for the MAS and TS_Q for the wrist flexor muscles (χ^2 [2] = 11.730, $P = .003$ and χ^2 [2] = 6.348, $P = .042$, respectively), passive wrist extension with extended fingers (χ^2 [2] = 6.419, $P = .040$), and FM-UE (χ^2 [2] = 10.360, $P = .006$). Post hoc analysis with Bonferroni correction showed a significant increase in FM-UE score between week 6 and week 12 post-intervention (median + 2, $Z = -2.680$, $P = .007$).

No significant correlation coefficients were found between the change scores within the first 6 weeks on the NC and EC of wrist hyper-resistance and the change scores on the clinical scales (Table 4). NC reduction within the first 6 weeks post-intervention showed a significant negative Pearson correlation coefficient to BoNT dose in the muscles affecting wrist and/or finger joints (r_p [17] = –0.56, $P = .016$) (Table 4 and Supplementary Appendix S3).

DISCUSSION

In this pre-experimental longitudinal study in a clinical cohort of adults with chronic stroke or CP with severe motor impairments,[26] we found that BoNT treatment in the wrist and/or finger flexor muscles significantly reduced the NC of resistance to passive wrist extension 6 and 12 weeks after treatment, while leaving the non-neural EC and VC unaffected. The reduction in NC within the first 6 weeks was moderately associated with the injected BoNT dose in the muscles affecting wrist and/or finger joints. Motor function of the upper paretic limb measured with FM-UE showed a significant increase between week 6 and 12 after BoNT treatment. Overall, no associations between the changes in NC and EC and the changes on clinical scales were found. No significant effects of BoNT were found in terms of upper limb capacity. These findings are in line with the previous systematic review[2] showing no association between the effects on the ICF level of body functions with the activities level by treatment of BoNT. Importantly, the present study suggests that in contrast to MAS and other clinical scales at body functions level,

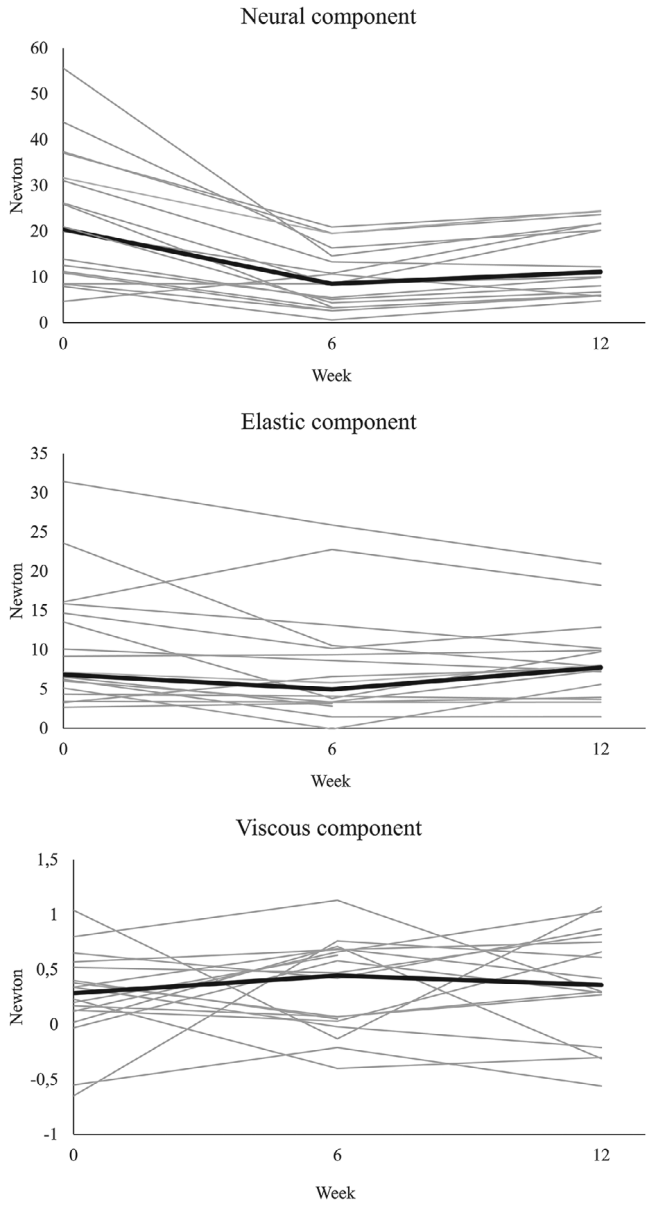

FIGURE 3 Neural and non-neural components of wrist hyper-resistance pre-intervention and at 6 and 12 weeks post-intervention. Bold line is median

the NeuroFlexor quantifies the separate effects of BoNT in the wrist and finger flexor muscles on the NC of wrist hyper-resistance. This instrumented measurement technique may have an added value in clinical practice for the precise evaluation of BoNT treatment in addition to recommended clinical scales.

Compared to a previous study by G verth et al[19] investigating the sensitivity of the NeuroFlexor to changes induced by BoNT treatment, we found a greater reduction in NC within 6 weeks post-intervention, which may be owing to a higher dosage of BoNT (present study: mean dose 288 ± 123 units Botox or Xeomin; G verth: mean dose 111 ± 54 units Botox). Evidence of a dose-response effect in the present study provides a further underpinning of aforementioned difference in reported treatment effects at the group level.

In contrast to the study of G verth et al,[19] we also investigated the resting force of the hand on the hand platform before onset of applied stretch with the NeuroFlexor and found significant reductions in this resting force at 6 and 12 weeks post-intervention. This resting force is assumed to be affected by gender and body length.[27] The resting force may also be influenced by the non-velocity dependent part of neural activation, that is, involuntary background activation.[9] Our results suggest that BoNT treatment not only reduces the velocity-dependent NC of wrist hyper-resistance but may also decrease the non-velocity dependent involuntary background activation. Note that the NeuroFlexor does not use electromyography (EMG) measurements, which prevents direct assessment of muscle activation. Construct validity of the NC was previously suggested in three ways, that is, by reduction of the NC after an ischemic nerve block, by showing a significant association with integrated EMG and by its velocity-dependency.[16] The NeuroFlexor method appeared to be construct valid with respect to the clinical modified Ashworth and Tardieu scales.[17]

The reduction of NC measured after 6 weeks, showing a clear dose-response relationship, was consistent with the non-significant reductions in the MAS and the Tardieu scale as well as with the increase of passive wrist extension within the first 6 weeks after treatment. Note that the NeuroFlexor may provide for quantitative effect determination of the NC in time beyond commonly used clinical scales. Clinical measures using ordinal scales, such as the MAS and Tardieu scales, may not capture small differences and with that probably underestimate associations in our small sample of participants. Moreover, the absence of significant associations between change scores of wrist hyper-resistance components and clinical scales suggests that the NeuroFlexor measures different constructs compared to currently used clinical scales. Measurements using the NeuroFlexor complement the clinical scales on the body functions level and offer quantitative outcome measures that associate with injected BoNT dose. Individual assessment of relative NC and EC contributions to wrist hyper-resistance may guide treatment/no treatment choices and a quantitative follow-up may allow for refining of BoNT dosing. The level of NC appears to be predictive for the treatment effect; however, this requires confirmation in a larger population. NeuroFlexor-based measurements and comparable instrumented measurement techniques may allow for a better understanding of the effects of BoNT with respect to different domains of the ICF, that is, the distinct effects on the level of body functions and the absence of effects on the activities level.[2] This is confirmed by results in the present study, although it should be noted that the present population of patients

TABLE 4 Correlation coefficients between changes scores within the first 6 weeks of the wrist hyper-resistance components and clinical scales, and botulinum toxin dose

	Analysis	ΔNC		ΔEC		BoNT dose wrist/finger	
		r	*P*	*r*	*P*	*r*	*P*
ΔNC	Pearson	1.00		0.11	.662	−0.56	.016
ΔEC	Pearson	0.11	.662	1.00		−0.28	.261
Wrist flexor muscles							
ΔMAS	Spearman	0.41	.093	0.19	.452	−0.10	.696
ΔTS_{Q}	Spearman	0.04	.986	−0.15	.551	0.35	.153
$\Delta TS_{R2\text{-}R1}$	Pearson	0.25	.320	−0.22	.386	0.38	.120
ΔWE_{FF}	Pearson	−0.39	.111	−0.11	.675	0.10	.698
Finger flexor muscles							
ΔMAS	Spearman	0.33	.177	−0.02	.924	−0.19	.448
ΔTS_{Q}	Spearman	−0.08	.754	−0.21	.396	0.36	.142
$\Delta TS_{R2\text{-}R1}$	Pearson	−0.21	.395	−0.24	.349	0.45	.060
ΔWE_{FE}	Pearson	−0.29	.238	−0.01	.981	0.00	.993
ΔPain average	Spearman	0.11	.675	0.20	.439	−0.35	.161
ΔPain worst	Spearman	0.12	.650	0.07	.780	−0.30	.220
ΔFM-UE	Spearman	−0.16	.529	−0.01	.967	0.42	.082
ΔARAT	Spearman	0.07	.799	0.15	.555	0.05	.844

Note: Values are *r*: Pearson product moment or Spearman's rank correlation coefficients; *P*: probability estimate, Δ outcome at week 6 post-intervention minus outcome pre-intervention.
Abbreviations: ARAT, action research arm test; BoNT dose wrist/finger, total dose botulinum toxin-A injected in muscles affecting wrist and/or finger joints; EC, elastic component; FM-UE, Fugl-Meyer motor assessment of the upper extremity; MAS, modified Ashworth scale; NC, neural component; TS_{Q}, Tardieu scale, quality score; $TS_{R2\text{-}R1}$, Tardieu scale, passive wrist extension angle at slow velocity (R2) minus passive wrist extension angle at fast velocity (R1); WE_{FE}, passive wrist extension, fingers extended (°); WE_{FF}, passive wrist extension, fingers flexed (°).
Gray-filled boxes indicate significant values.

showed hardly any arm and hand function, resulting in floor effects of the ARAT measuring arm and hand capacity on the activities level. We found a small significant increase in FM-UE score between 6 and 12 weeks post-intervention. This increase, however, is below the smallest detectable difference of approximately 7 points on the FM-UE.[24,28] Whether BoNT affects voluntary movements in patients with a range of motor impairments was not addressed in this study.

Study limitations

We conducted a pre-experimental, non-blinded observational study in a small mixed population, presenting severe motor impairments, without a control group. Lack of blinding may affect the MAS and Tardieu scale scores but is unlikely to affect the outcomes of wrist hyper-resistance components. Moreover, only two patients had first-ever BoNT treatment, whereas the other 16 patients received multiple previous BoNT injections. Despite the limitations, we were able identify changes of individual components of wrist hyper-resistance after BoNT treatment.

A possible drawback of the NeuroFlexor for the evaluation of BoNT treatment is that 40° passive wrist extension is needed to comply with the original measurement protocol using a fixed 50° wrist extension range, regardless of the patients' passive range of motion. Further research is needed into the applicability of this device, as well as the validity and reliability of the outcomes, in a population with restrictions of the passive range of wrist extension.

CONCLUSIONS

Using an instrumented approach quantifying the separate components of wrist hyper-resistance, BoNT treatment in the wrist and/or finger flexor muscles in adults with stroke or CP is suggested to provide a dose-dependent reduction of the NC of resistance to passive wrist extension, while leaving the non-neural EC and VC unaffected. Instrumented quantification of wrist hyper-resistance components may have an added value for BoNT treatment indication and evaluation in clinical practice.

More data are required to conclude on the predictive value of NeuroFlexor-based measurements for BoNT outcome. Identifying responders and non-responders of BoNT treatment based on the components of hyper-resistance, allows for the effects of BoNT on NC to be

further investigated in a double-blinded, randomized, stratified, placebo-controlled trial with repeated measurements. Stratification at baseline should be based on the neural and non-neural components of wrist hyper-resistance. Frequent, serially applied repeated measurements at fixed time points within the first 6 weeks are needed to better understand the mechanisms underlying the longitudinal reductions in neural and non-neural components of wrist hyper-resistance caused by BoNT and to further address its precision and responsiveness to change in order to conclude on its potential for individual tuning of dose. In addition, further research is needed to examine the effect of BoNT on wrist hyper-resistance of different origins, for example, chronic stroke versus CP. Further work on the construct validity of the NeuroFlexor with respect to the underlying components of wrist hyper-resistance and its translation into velocity-dependent and non-velocity-dependent neural and non-neural components is also needed, for example, by comparing of the NeuroFlexor with methods that encompass EMG enabling direct measurements of muscle activity.

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DISCLOSURES

The authors report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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