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REPORT - MAJOR RESEARCH PROJECT

Early Botulinumtoxin Treatment for Poststroke-Spasticity

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Abstract

OBJECTIVES: To investigate the effectiveness of Botulinumtoxin (BoNT) treatment during the subacute post stroke phase.

METHODS: 12-month data collected in the early rehabilitation ward of the neurology department in Charite - University hospital Berlin, was retrospectively analyzed.

SUBJECTS: 16 Stroke patients with paresis and evolving upper limb spasticity were included. Patients undergoing BoNT therapy (n = 9) were comparatively evaluated against non-treated patients exhibiting similar indications for BoNT treatment (n = 7).

INTERVENTION: BoNT-A (Xeomin®) was injected into upper limb musculature according to a conservative injection protocol (approximately one-third of standard dosage) within four weeks after stroke event (M = 16 days, SD ± 5 days).

MEASURES: Baseline and follow-up assessment included stroke severity (National Institutes of Health Stroke Scale), activities of daily living (Barthel Index) and sensory - motor functioning (Early functional abilities, Motricity Index, Hermagor Scale). The primary outcome measure was muscle tone of the upper limb musculature assessed with the modified Ashworth scale (MAS).

RESULTS: Pre - post changes were not significantly different between groups. Within group analysis revealed a statistically significant increase in elbow MAS from baseline to follow-up for the control group only.

CONCLUSION: A beneficial effect of early BoNT treatment became apparent. Whereas untreated patients evidenced an increase in muscle tone, the MAS score remained stable for the treatment group. The outcome corroborates recent findings on the effectivity of BoNT during the subacute post stroke phase.

Introduction to the research question

Stroke related disability is a major factor impeding patients return into the workforce and reducing health related quality of life after discharge.[1] In particular, motor related morbidities are a significant contributor to physical limitations, deformities and pain and affect approximately 50% of stroke survivors.[2] The high prevalence of post stroke motor impairments is a major public health concern presumably associated with the predominant occurrence of ischemic strokes affecting the vascular territory of the middle cerebral artery.[3] Another underlying factor might be the relative large area of neuronal tissue devoted to somatic motor control and its extensive subcortical and spinal pathways.[4, 5] The significance of functional impairments after cerebrovascular event is reflected in the accompanying socioeconomic burden. Herein, the latest report from the American Heart Association numeralized the indirect costs of stroke, which are mainly due to motor related disability and the corresponding loss of productivity as well as independence to a total of 25.5 Billion US dollars for the United States.[6]

The clinical picture which characterizes post-stroke impairments in motor function is the upper motor neuron syndrome (UMNS).[7] Pathophysiologically, UMNS after cerebrovascular insult results from damage to cortical motor neurons or their descending axonal connections. This loss of functional efferents onto spinal circuitry leads to an initial phase of flaccid paralysis in the affected limb. However, in the following days or weeks intumescential motor neurons become active again and give rise to a pattern of motor abnormalities known as positive upper motor neuron symptoms.[4] One of these subacute features is muscular hypertonicity. Up to now a variety of spasticity definitions exist trying to capture the essence of this intricate clinical entity. A notably often cited description was provided by Young who defined spasticity as “a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes that results from abnormal intra-spinal processing of primary afferent input”.[8] The specific mechanisms underlying the evolution of muscular hypertonicity is not completely understood and similarly to the terminological discussion, research generated a number of explanatory models. However, in more general terms it is assumed that a lesion-induced imbalance of excitatory and inhibitory signals into ventral horn motor neurons is responsible for the hypertonic aberrancy.[9] The prevalence rates of spasticity in stroke survivors were described as highly variable with estimates ranging from 2% to 42.6%. More stables approximations were reported in a recent epidemiological literature review, wherein the time course of spasticity development was grouped into three phases. During the subacute post stroke phase covering week one till week four after stroke estimates ranged from 4% to 27% and increased in the post-acute stage to 19% to 26.7%. In the chronic phase (three month post stroke) prevalence rates raised further to a range between 17% and 42.6%.[10]

Taking a patient centered perspective it becomes apparent that next to the primary pathology additional complications arising from spastic musculature contribute significantly to disease burden. Herein, mechanical pain caused by spasticity induced muscle shortening and sensory disturbances is the third leading cause of chronic post stroke pain syndromes and is, in itself related to cognitive decline and affective problems.[11, 12] Further, the impeding immobilization of limbs hinders nursing, personal hygiene and independent grooming. In consequence afflicted individuals suffer from impairments in activities of daily living and decreased quality of life.[13] Similarly, rehabilitative success is negatively affected by progressive loss of physical flexibility which restraints functional improvement after stroke event.[14] Another concomitant pathology frequently encountered in patients with spasticity are contractures. These soft tissue abnormalities are a consequence of loss of elastic properties and permanent shortening of muscle tissue which aggravates muscular hypertonicity and thus further impedes functional recovery.[10]

Therapeutic approaches in spasticity management focus mainly on ameliorative treatment as no curative therapy has yet been found. Herein, the ultimate goal is restoration of patients functional independence to the highest possible degree. Specialized treatment paradigms include physically orientated approaches like diverse strategies for muscle stretching, training of muscle strength and occupational therapy. More invasive interventions are conducted by medical specialists in neurosurgical departments involving implantation of intrathecal baclofen pumps or selective lesioning of nerve roots or fibers. Pharmacological interventions encompass central muscle relaxants like benzodiazepines or more focused drug treatments selectively targeting peripheral muscles. The choice for a defined rehabilitative approach is based on clinical impression, patient goals and should take into account risk factors and contraindications.[15, 16] However, multimodal strategies have shown superior utility in clinical studies. Herein, manual therapy combined with intramuscular botulinum toxin (BoNT) injection in case of focally distributed hypertonicity represents the rehabilitative “Gold-standard”.[10] Efficacy of this therapeutic modality was proven by several randomized controlled trials (RCTs), showing improvement at level of targeted pathology, in global outcome measures and pain in patients with upper limb spasticity.[17-19]

Botulinum toxin modulates the excitability of peripheral muscles by presynaptic inhibition of efferent signaling. After intramuscular injection the neurotoxin binds to surface receptors present on the neuronal membrane of cholinergic nerve terminals and exploits the vesicular recycling system to enter the cell. Inside, the acting polypeptide of BoNT (the light chain domain) cleaves the critical SNARE protein which under physiological conditions ensures fusion of synaptic vesicles to the active zone prior to exocytosis. Correspondingly, cholinergic neurotransmission from nerve terminal to motor endplate is blocked and somatic motor commands are inhibited. BoNT activity is halted approximately three month

after drug administration via ubiquitylation and degradation of the light chain domain by the cellular proteasome system and accordingly nerve transmission is resumed.[20]

According to clinical guidelines BoNT treatment is initiated once spasticity becomes phenomenologically apparent which happens most commonly during the chronic post stroke phase. However, at that time established hypertonicity already interferes with cerebral reorganization and results in disturbed body image, balance and gait.[21-23] Moreover, developing contractures might have a detrimental effect on the functionality of muscles and tendon organs independent of the underlying spasticity. In this regard earlier dispatch of treatments aimed at reduction of muscular hypertonicity might preclude development of secondary intricacies and correspondingly improve functional outcome and quality of life. Therefore reliable identification of at risk patients by means of predictive factors is imperative for prompt treatment initiation. A recent literature survey by Wissel et al. addressed this issue by synthesizing outcomes of 7 studies including data on 801 patients. The review identified five variables that when present early after stroke, constitute an elevated risk for spasticity during the chronic post stroke phase. Among them, occurrence and degree of paresis were shown to be associated with the highest risk for later spasticity. Next, increase in muscle tone, even if only in the moderate range (MAS $\geq$ 1) were further predictive for chronic spasticity. Also, measures of functional disabilities, quality of life and lesion volume have shown a contribution to elevated muscle tone. Conclusively, the authors support early initiation of specialized treatment approaches based on patients risk profile.[24]

In our neurological rehabilitation ward, stroke patients with signs for impeding spasticity undergo intramuscular treatment with Botulinumtoxin as part of routine practice. Due to severe pain or developing malposition of the upper extremities selected patients were treated with BoNT already within four weeks after stroke event. In the current report, data of these patients is retrospectively summarized and comparatively evaluated against patients exhibiting similar treatment indications for intramuscular BoNT but declined therapy or displayed contraindications. Since no guidelines for early interventions exist a very conservative dosage of neurolytic agent was used (approximately one-third of the recommended dosage). Our research question asked for the effectivity of BoNT administration within one month following stroke event. We hypothesized that early BoNT treatment leads to decreased spasticity thus conveying between group differences in MAS.

Materials and Methods

Data sources

12 month data collected in the early rehabilitation ward of the neurology department in Charite – University hospital Berlin – was retrospectively analyzed. Ethical approval was granted by the institutional review board. Data abstraction was based on neurologists' written report and physical assessment at admission and discharge.

Materials

National Institutes of Health Stroke Scale (NIHSS). The NIHSS is an acute assessment instrument and measures severity of symptoms following cerebrovascular accidents. Eleven items score level of consciousness (0 - 3), horizontal eye movement (0 - 2), visual field (0 - 3), facial palsy (0 - 3), motor function of arms and legs (0 - 4), limb ataxia (0 - 2), sensory functioning (0 - 2), language (0 - 3), speech (0 - 3), extinction and inattention (0 - 2). The total score is derived from summation over the respective items which categorize severity of impairments from 0 (no stroke symptoms) to 2, 3 or 4 (severe stroke symptoms).[25]

Barthel Index. The Barthel index is a measure of patients ability to perform activities of daily living. Ten items are scored from 0 (no independence / unable to perform the task) up to 15 (full independence / task performance without external assistance). The assessment includes following domains; feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing.[26]

Early functional abilities (EFA). The EFA scale is an assessment tool designed for patients with cerebral lesions hospitalized in early neurological rehabilitation wards. The original scale consists of 20 items grouped into four domains; vegetative, fascio-oral, sensorimotor and cognitive function. Scoring is based on a 5 point categorical scale from 1 (no function) to 5 (full function). For the current study only the sensorimotor subdomain was used in later analysis.[27]

Motricity Index. The motricity index evaluates the degree of motor impairments present in upper and lower extremities as consequence of paresis or plegia. Patients are required to execute a number of movements; arm function is assessed by the pinch grip, elbow flexion and shoulder abduction; leg function is assessed by ankle dorsiflexion, knee extension and hip flexion. The ability to perform each movement sequence is graded from 0 (no movement) to 33 (normal movement). Summing over the items

gives a total score and separate scores for the lower and upper extremities. For the current study only the upper extremity subscale was used.[28]

Functional assessment of hand (Hermagor Scale). An unpublished scale was used to assess hand function according to manual abilities in performing actions important for daily living. Functional abilities of the impaired extremity were graded on a 5 point categorical scale; 1 = no functions in affected upper extremity, 2 = affected arm / hand can be used to fixate a sheet of paper on table, 3 = affected hand performs gross motor actions necessary to hold larger objects, 4 = affected hand can be used as assistance for bimanual work; arm can be moved against gravity, 5 = affected upper extremity is functional in performing bimanual tasks with only minor restrictions (slight tremor, subtle signs of bradykinesia, minimal fluctuations in muscle tone).

Modified Ashworth Scale (MAS). The modified Ashworth scale assesses velocity dependent resistance against passive movement. Muscle tone is scored on a 5 point scale from 0 (no increase in muscle tone) to 5 (limb rigid in flexion or extension). Separate assessments are made for each joint. Psychometric properties of the MAS were evaluated in numerous trials with stroke patients undergoing BoNT therapy for focally distributed spasticity. Herein, one-point changes in muscle tone were considered as clinically significant improvements in muscle tone. In the current analysis measures were taken for wrist, elbow and shoulder musculature.[29, 30]

TOAST classification. Classification of stroke type was based on the TOAST classification system. Stroke incidents are categorized according to one of five etiological mechanisms; large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology.[31]

Lesion volume. Volumetric analysis of the amount of lesioned tissue was based on patients computerized tomography (CT) or magnetic resonance imaging (MRI; T2 weighted) data obtained during acute stroke imaging. Herein, transversal planes were used to isolate the imaging slice with the largest depiction of cerebral lesion. Next, the width (x axis) and length (y axis) of hyperintense (MRI) / hypointense (CT) tissue was measured with an electronic ruler. Lastly, the height (z axis) of the lesion was determined by searching for the most dorsal and the most ventral plain containing hyperintense (MRI) / hypointense (CT) tissue and multiplying the number of slices with lesion marks by the thickness of the slices. Total volume was calculated by multiplication of the three coordinates ($V^3 = x * y * z$).

Patients

16 patients with documented cerebrovascular accident on neurological and radiological examination were included. All patients presented with unilateral monoparesis affecting upper limb muscles. Eligibility for BoNT treatment was evaluated by an interdisciplinary team including a senior stroke specialist, a ward physician, a physical therapist and an occupational therapist and was based on persistence of upper limb spasticity for five consecutive days associated with malpositioning and pain. Out of the 16 contemplable patients nine were treated with BoNT, the remaining seven patients declined therapy or were unsuitable due to coagulopathy. Before treatment instigation, patients were briefed about possible side effects and harms and signed the informed consent.

Treatment protocol

The treatment group received BoNT-A (Xeomin®) diluted with sodium chloride.[32] Treatment initiation started within four weeks after stroke event, the mean time interval from stroke to BoNT was 16.3 days (min = 10 days, max = 24 days). An experienced neurologist injected following amounts (M ± SD in international units (IU)) into the affected muscles: flexor digitorum superficialis and profundus (23.7 ± 11.0), flexor carpi radialis and ulnaris (35.0 ± 7.1), biceps brachii (26.2 ± 6.6), brachioradialis (16.0 ± 5.4), brachialis (16.0 ± 12.2), pectoralis (20.3 ± 10.1), suprascapularis (8.0 ± 0.0). The average total amount was 77.7 IU ± 24.6 IU. The patient specific dose was chosen based on clinical presentation and body weight. Furthermore, all patients received physical and occupational therapy according to clinical guidelines throughout their hospitalization.

Procedure

Acute stroke patients were hospitalized and underwent an emergency imaging routine. Barthel index and NIHHS were assessed by nursing personal during patients stay in the stroke unit. After relocation to the early neurological rehabilitation ward experienced physical and occupational therapists administered following assessments; Early functional abilities, Motricity Index, Hermagor Scale and Modified Ashworth Scale. Next, eligible and consenting patients received intramuscular BoNT. The initial physical assessment procedure was repeated before patients were discharged from hospital. The remaining variables used in the current study were abstracted from medical reports.

Statistical analysis

All statistical analysis were performed using SPSS 21.0 with significance level $P < 0.05$ (2-tailed).[33] Graphical representations were made with R-Studio and SPSS 21.0.[34] Univariate group

comparison was computed with ANOVA and ANCOVA or nonparametric equivalents when indicated. Differences within groups were calculated by paired samples t-tests and Wilcoxon signed-rank tests. Bivariate statistics were computed for analysis of correlations between time from stroke till BoNT treatment and changes in MAS scores.

Results

Baseline demographics, diagnostic variables and time intervals between stroke, pre- and post-assessments and BoNT treatment are depicted in Table 1. The groups were considered homogenous in all respects except for differences in TOAST classification.

Table 1. Baseline characteristics

	BoNT	Control	*P*
n	9	7	
Age in years, M ±SD	67 ±10, range 49-82	76 ±9, range 66-90	.087[1]
Female gender, n	3 (33%)	3 (43%)	.696[2]
Smoking, n	2 (22%)	0	.182[2]
Arterial Hypertension, n	8 (89%)	5 (71%)	.375[2]
Diabetes mellitus, n	3 (33%)	0	.090[2]
Hypercholesterolemia, n	6 (67%)	2 (29%)	.131[2]
TOAST classification, n			
large-artery atherosclerosis	**6 (67%)**	**1 (14%)**	**.036[2]**
cardioembolic	**1 (11%)**	**5 (71%)**	**.013[2]**
small-artery occlusion	0	0	-
other determined etiology	0	1 (14%)	.242[2]
undetermined etiology	2 (22%)	0	.687[2]
Stroke diagnosis, n			
ischemic	6 (67%)	5 (71%)	.838[2]
hemorrhagic	0	1 (14%)	.242[2]
secondary hemorrhagic	3 (33%)	1 (14%)	.383[2]
Lesion volume in cm^3, M ±SD	279.6 ±125.4	187.8 ±235.7	.064[3]
Left hemiparesis, n	6 (67%)	5 (71%)	.838[2]
Barthel Index, M ±SD	12 ±11	14 ±9	.724[1]
NIHSS, M ±SD	14 ±4	13 ±5	.518[1]
EFA sensory motor domain, M ±SD	13.2 ±2.1	13.3 ±5.6	.312[3]
Motricity Index, M ±SD			
pinch grip	0.0 ±0.0	3.1 ±8.3	.257[3]
elbow flexion	1.0 ±3.0	2.0 ±5.3	.783[3]
shoulder abduction	0.0 ±0.0	2.0 ±5.3	.257[3]
Hermagor scale, M ±SD	1.0 ±0.0	1.3 ±0.8	.257[3]
Interval in days, M ±SD			
Stroke – T_0	4.3 ±2.2	3.9 ±1.2	.432[1]
T_0 – T_1	19.6 ±7.0	22.1 ±6.4	.456[1]
Stroke – BoNT	16.3 ±4.8	-	-
T_0 – BoNT	11.8 ±5.2	-	-
BoNT – T_1	7.8 ±4.7	-	-

BoNT, Botulinum Toxin treatment; EFA, early functional abilities; NIHSS, National Institutes of Health Stroke Scale; Note: bold face print denotes p-value < .05.

[1] ANOVA F – test

[2] Pearson Chi^2- test

[3] Wilcoxon signed-rank test

In this regard, there were significantly more patients with stroke due to macroangiopathy in the treated group ($Chi^2 = 4.39$, $P = 0.036$) and significantly more patients with stroke of cardioembolic origin in the untreated group ($Chi^2 = 6.11$, $P = 0.013$). Also, lesion volume displayed a trend (Wilcoxon W = 42, $P = .064$) for greater cerebral lesions in the BoNT group. Initial analysis of treatment effects was conducted with an ANCOVA model to investigate between group differences in muscle tone at discharge corrected for baseline variability. Two separate ANCOVAS, one for elbow and one for wrist musculature were used with MAS scores at post assessment as dependent variable, group as independent variable and MAS scores at baseline as covariate. There were no significant effects for wrist musculature. For elbow musculature a trend became apparent for the interaction term between group (BoNT, Control) and covariate (MAS baseline scores) ($F(1,2) = 3.547$, $P = .059$). The baseline corrected MAS score at discharge were non-significantly higher for the BoNT group (M = 2.35, SE = 0.30) in comparison to the untreated group (M = 1.88, SE = 0.50), suggesting that with equal baseline MAS scores (M = 1.44) the treated group would show higher elbow MAS values at discharge. Next, uncorrected between group and within group analysis were conducted. Table 2 displays results for the elbow and wrist MAS as measured at pre- and post- time points, separately for each patient group.

Table 2. Primary outcomes

	BoNT			Control				
	Pre	Post	*P*	Pre	Post	*P*	P_{Pre}	P_{Post}
MAS elbow	2.00 (±1.73)	2.44 (1.59)	.347[1]	**0.71 (±1.11)**	**2.00 (±0.82)**	**.049[1]**	.146[3]	.513[2]
MAS wrist	2.11 (±1.83)	2.22 (±1.39)	.834[1]	0.71 (±1.11)	1.86 (±0.90)	.066[1]	.132[3]	.558[2]

MAS, Modified Ashworth Scale; BoNT, Botulinum Toxin treatment; Note: values represent M (±SD); bold face print denotes p-value < .05.

[1] paired-sample T-test

[2] ANOVA F-test

[3] Wilcoxon rank-sum test

Univariate between group statistics at both assessments revealed absence of systematic variation, indicating equality in MAS scores at baseline and follow-up. Restriction of analysis to within group differences revealed a significant time effect for the control sample in the elbow MAS between pre and post assessment ($T(6) = 2.471$, $P = .049$) with higher scores at discharge (M = 2.00, SD = 0.82) in comparison to baseline (M = 0.71, SD = 1.11). Furthermore, the control group showed a trend in wrist MAS ($T(6) = 2.249$, $P = .066$) having higher discharge scores (M = 1.86, SD = 0.90) in comparison to baseline assessment (M = 0.71, SD = 1.11). For the BoNT condition within group differences did not achieve statistical significance ($T_{MAS\ wrist}(8) = 0.217$, $P = .834$; $T_{MAS\ elbow}(8) = 1.001$, $P = .347$.), indicating similar MAS values across time. A graphical representation of the pre - post differences in MAS for both patient groups can be found in Figure 1.

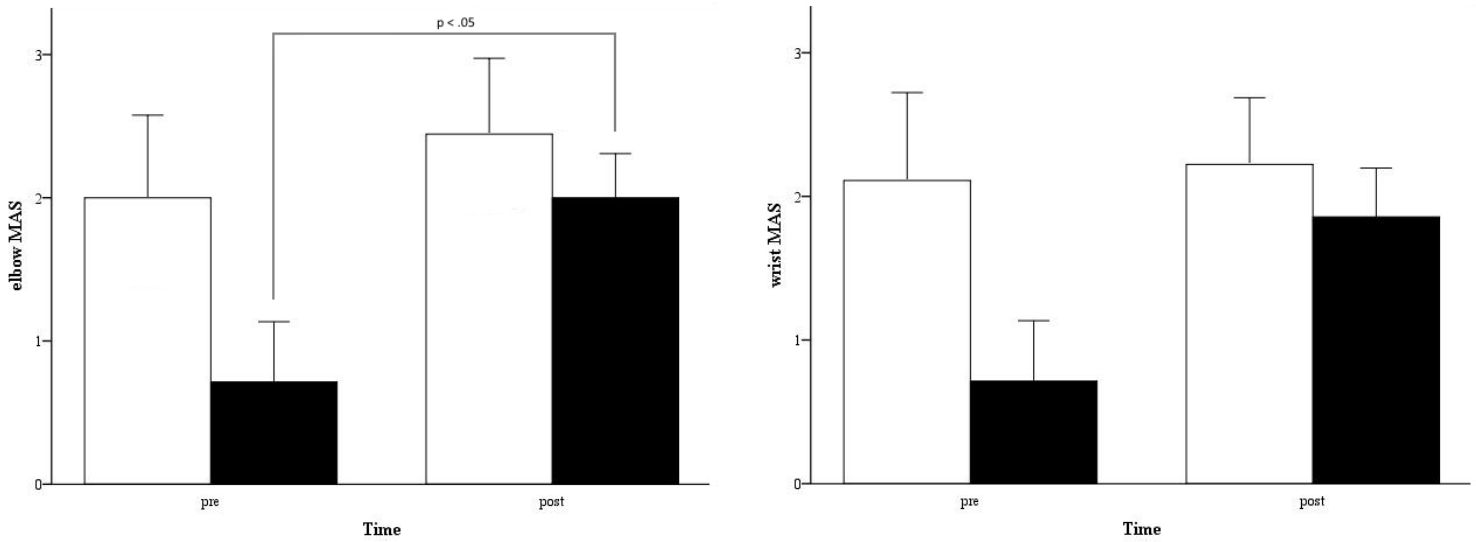

Figure 1. Changes in mean MAS scores from pre to post assessment for BoNT treated (white stacks) and untreated (black stacks) patients; Note: Error bars represent ± 1SE.

Finally, calculation of bivariate statistics between the time from stroke to BoNT treatment and the changes in MAS revealed a positive correlation of large effect size for elbow (r = .716, n = 9, *P* = .030) and for wrist musculature (r = .731, n = 9, *P* = .025) wherein longer latencies are associated with an increase in MAS (see Figure 2).

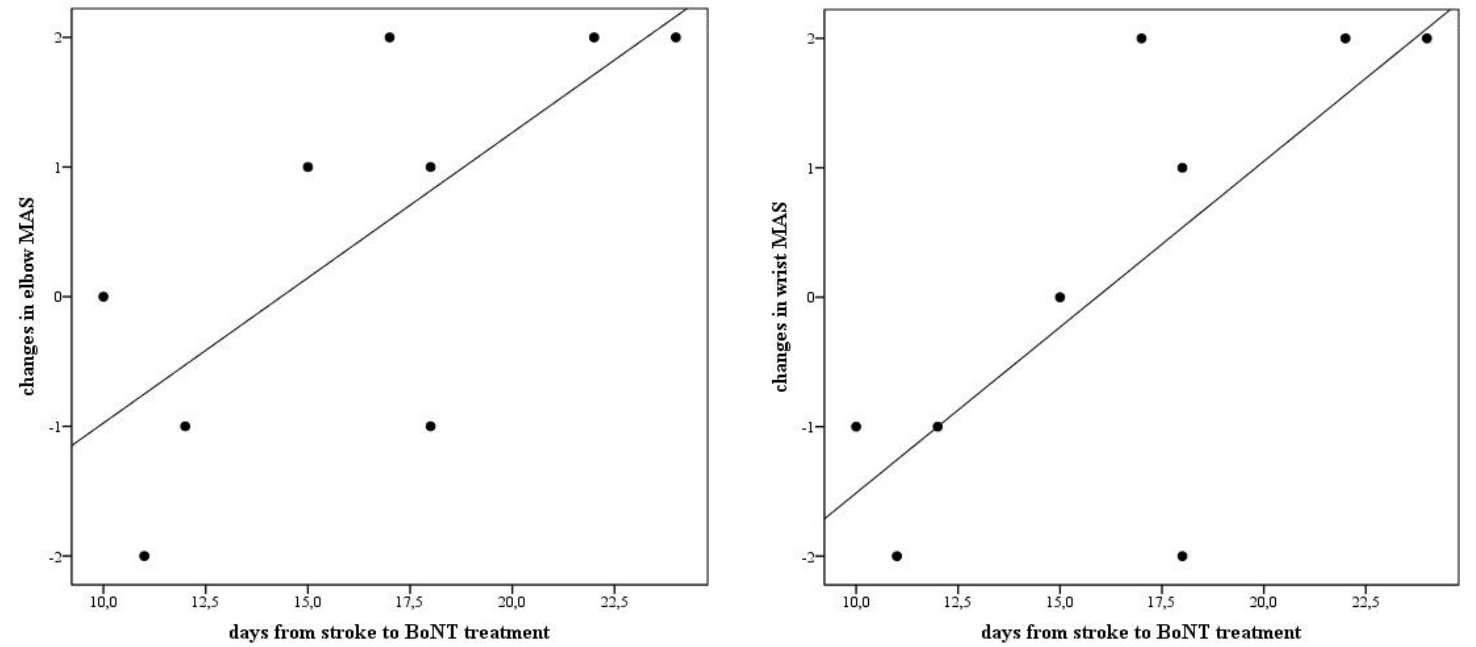

Figure 2. Scatterplot between changes in mean MAS scores from pre to post assessment and time from stroke to BoNT treatment. Diagonals represent linear fit between x and y values ($y_{elbow\ MAS} = -3.21 + 0.22x$, $r^2 = 0.51$; $y_{wrist\ MAS} = -4.07 + 0.26x$, $r^2 = 0.53$).

Discussion

The current study analyzed retrospective data to evaluate the effectivity of BoNT treatment instigated during the subacute post stroke phase. Although our primary hypothesis, stating salutatory benefits in terms of decreased muscle tone for patients receiving the active treatment was not confirmed, interesting results were obtained.

First, contrary to our initial prediction the data showed no significant time effect stating decreased MAS scores for the BoNT group. In contrast, a non-significant trend demonstrated increased muscle tone in elbow musculature at follow up for treated patients using a baseline corrected ANCOVA model. However, group-wise analyses of changes from pre- to post-assessment revealed an increase in MAS scores for untreated patients, being significant for elbow musculature and narrowly missing the predetermined p-value for wrist musculature. For the active treatment group no such increments in muscle tone were apparent instead MAS score remained stable throughout the assessment period. Thus, whereas our initial prediction could not be directly validated we could nevertheless show a statistically confirmed benefit denoted as stabilization of muscle tone scores for the BoNT group. Beyond that, an exploratory correlational analysis restricted to the BoNT group revealed a positive association of large effect size between the time interval from stroke to treatment and pre-post changes in MAS scores. This auxiliary finding suggests that earlier administration of BoNT leads to superior effects and supports the scientific literature arguing for prompt treatment instigation.[14]

4% to 27% of stroke patients experience development of spasticity within six weeks after cerebrovascular event.[24] The pathological increase in muscle tone is part of the UMNS and is hypothesized to be due an imbalance between excitatory and inhibitory signals inside spinal motor neurons culminating in abnormal joint posture, contractures, pain, functional disability and quality of life impairments.[9] Clinical management by means of physical therapy combined with intramuscular BoNT is the method of choice for focal spasticity.[35] In specific, BoNT therapy has evidenced superiority in terms of muscle tone measures, pain, activities of daily living and quality of life.[16] It is assumed that its effectivity is a function of treatment initiation time, whereby earlier application of BoNT after stroke event is associated with better outcomes.[14] However, in clinical practice prevailing treatment regimens stipulate a comparatively late instigation of BoNT therapy, starting weeks to month after primary insult. Thus, at the time of drug administration dysfunctional movement patterns are incorporated into patients motor routine and contractures become apparent competing with functional rehabilitation and cerebral reorganization following stroke event.[10, 14]

The application of BoNT treatment during the subacute post stroke phase and its potential to prevent secondary complications was investigated by three scientific publications. Firstly, Cousins et al. conducted a phase-II RCT exploring the effectivity of early BoNT already three week after stroke event.[23] Upper limb Spasticity was assessed with surface electromyography (sEMG) at five measurement points throughout the study period (baseline, one, four, eight, twelve and twenty weeks follow-up). The treatment protocol utilized BoNT dosages below clinical recommendations and comprised three experimental groups (saline control, one-quarter and one-half of the standard BoNT dosage). No time effect was found differentiating between placebo treatment and active treatment in sEMG or Action Research Arm Test (ARAT). Nevertheless, subsample analysis confined to patients with no arm function at baseline (ARAT = 0) showed substantial but non-significant functional increments for both BoNT groups. Moreover, spasticity assessments revealed an advantage for the treated samples compared to controls in measures of muscle tone. The authors concluded that early treatment instigation using a conservative dosage protocol yields functional benefits for severely affected patients and might prevent worsening of spasticity in the subacute post stroke phase. The second study on early treatment investigated the effects of BoNT injected into lower arm musculature six weeks after cerebrovascular insult.[36] Patients were dichotomized into to treatment or no-treatment groups and assessed for spasticity (MAS, REPAS), motor functioning (Fugl-Mayer Scale), disability ratings and pain at three measurement time points (baseline, one month and six month follow-up). In contrast to the study by Cousins et al. the results signified superior outcomes for the BoNT treated group across both assessment schedules, with progressively decreasing MAS scores, pain ratings and disability measures.[23] Conclusively, the positive effect on muscle tone and extrapolation of motor improvements onto daily living abilities were attributed to prevention of imminent contractures by early treatment. Another paper on early BoNT administration examined the impact on lower limb musculature with an injection timeframe of four to six weeks after stroke event.[37] Similar to Cousins' approach, the experiment was saline controlled and a rather conservative dosage was used for the active treatment group.[23] Patients underwent comprehensive assessments including gait analysis, 6-min walking test, Fugl-Meyer scale, MAS, sEMG and modified Barthel index at baseline and at two follow-up appointments (four and eight weeks). Marginal improvements were apparent in motor functioning and daily living activities for both groups throughout the study period. Nevertheless, statistically significant differences between BoNT and saline treatment were evident at week eight, showing an apparent benefit for the active treatment. Similarly, treated patients showed an advantage over controls for measures of spasticity and in the gait analysis at second follow-up. In conclusion, the authors ascribed the resulting group differences in functional measures and muscle tone of the lower limb musculature to the beneficial effects of BoNT treatment on concomitant physical therapy during the acute rehabilitation phase.

The encouraging results obtained in aforementioned studies could be corroborated by the current retrospective data analysis. In accordance with the results from Cousins et al. we observed stabilization of muscle tone for paretic patients treated with minuscule amounts of BoNT.[23] Compared to untreated patients which showed progressive elevation in MAS, this outcome signifies a clinically relevant advantage for treatment instigation already in the subacute post stroke phase.[29] However, in contrast to the experimental studies we did not find evidence for an impact of changes in muscle tone on motor performance or functional abilities. The reason for the null findings is most likely related to the brief and highly variable assessment timeframe ($M_{T0\text{-}T1}$ = 20 days, $SD_{T0\text{-}T1}$ = 7 days) and scheduling of BoNT injections which took place halfway through the assessment period ($M_{T0\text{-}BoNT}$ = 12 days, $SD_{T0\text{-}BoNT}$ = 5 days). Consequently, there were only a few days for functional improvement taking into account the pharmacokinetics of the drug.[32] Tentative support for this assumption can be found in the results from Hesse et al.[36] Herein, the first follow-up assessment (four weeks after treatment) did not show significant differences on measures of disability and pain. Similar temporal patterns were evident in the study by Tao et al.[37] Thus it might be assumed that a hypothetical second follow-up assessment would have evidenced changes in functional outcomes.

Limitations and Conclusion

There are several shortcomings in the current report. The most notable limitation is the retrospective nature of the analysis which resulted in considerable heterogeneity with regard to patient characteristics, assessment and treatment time points. For example, the age difference between groups although not statistically significant could have affected the development of spasticity. Similarly, there could be a confounding effect of baseline MAS differences affecting the outcome. On the other hand, the chosen retrospective analysis has the advantage of giving an unbiased view on the evolution of spasticity in treated and untreated patients, as the objective of data collection was not related to the effectiveness of the pharmaceutical agent.[38] Secondly, the short time frame of the assessment period constricted the analysis of treatment effects. As argued above, evolution of functional benefits might have been observed at a later time point following BoNT therapy but did not show up during our follow-up assessment. Furthermore, postponed assessment might have given clearer evidence in favor of our initial research hypothesis by showing decreased muscle tone scores for the treatment group.

Nevertheless, it can be conclusively stated that albeit the methodological constraints and minimal dosage of therapeutic agent the current report evidenced a positive effect on spasticity measures of upper limb musculature. Taking into account results from former studies on subacute BoNT application it might be concluded that early therapy following cerebrovascular event is a safe and advisable treatment

approach for combating pain and development of contractures in selected patients. A prospective study for confirmation of the herein found effects including adequate control patients and comprehensive outcome measures is in preparation.

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