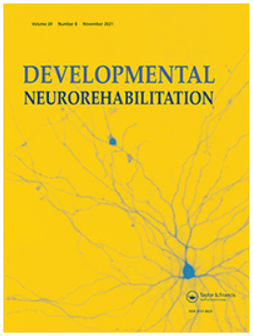

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Botulinum Toxin Type A in the Spasticity of Cerebral Palsy Related to Congenital Zika Syndrome: An Observational Study

Giulia Armani-Franceschi[a], Cleber Luz[a], Pedro H. Lucena[b], Danilo d'Afonseca[a], Henrique Sales[a], Alessandra L. Carvalho[a], Isadora C. Siqueira[c], Karine Silva[a], Sandra Portuense[a], Larissa Monteiro[a], Igor D. Bandeira[a], Ailton Melo[a], and Rita Lucena[a]

[a]Universidade Federal da Bahia, Salvador, Brazil; [b]Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil; [c]Fundação Oswaldo Cruz, Salvador, Brazil

ABSTRACT

Purpose: Investigate the effect of botulinum toxin type-A (BoNT-A) on spasticity and motor performance in children with Cerebral Palsy (CP) related to Congenital Zika Syndrome (CZS).

Methods: Prospective longitudinal observational study of 34 children with CP referred for BoNT-A treatment. Outcomes were evaluated with a muscle tone assessment scale (Modified Ashworth Scale – MAS) and the Patients' Global Impression of Improvement (PGI-I) scale.

Results:: Mean age was 32.06 ± 3.07 months and 85% were classified as Gross Motor Function Classification System (GMFCS) V. Primitive reflexes were present in 56% of the sample. The majority of the parents (97.9%) reported improvement in range of motion or reduction in spasticity after treatment with botulinum toxin. No side effects were recorded. When compared to the baseline, median reduction in the MAS was 0.5 (IQR = 0).

Conclusions: The findings of this study suggest that BoNT-A may effectively promote functional improvements and reduce muscle tone, improving the child's and family's quality of life.

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KEYWORDS
Botulinum toxin type A; cerebral palsy; congenital Zika syndrome; Zika virus

Introduction

The Zika Virus (ZIKV) is a single-stranded RNA arbovirus of the *Flavivirus* genus and *Flaviviridae* family; its hosts are humans and hematophagous arthropods, generally of the genus *Aedes*, which are also responsible for the transmission of other infections, such as Dengue and Chikungunya.[1–3]

A cohort of children with microcephaly secondary to ZIKV demonstrated high prevalence of spastic or dyskinetic cerebral palsy with severe motor and cognitive impairment and hyperexcitability to tactile and proprioceptive stimuli. Carvalho et al. showed that in the cohort, 88.6% of the children had microcephaly, 86.5% were classified with a GMFCS IV or V, and 97.6% of the children had an extremely low motor score.[4] Highly atypical motor patterns have been observed in these children and spasticity is considered to be one of the most significant challenges to rehabilitation. Persistent increased tone interferes with positioning and hygiene, causes pain and discomfort, and is associated with atypical posture, increased risk of deformities and joint problems due to atypical muscle growth.[5]

Over the last two decades, botulinum toxin type A (BoNT-A) has been established as an important option for the treatment of several neurological disorders.[6–8] Among other disorders, BoNT-A has been used to reduce spasticity in children with cerebral palsy by reducing tone, preventing contractions and improving functionality.[9] The atypical motor patterns observed in children infected by ZIKV in the intrauterine period have been associated with neurogenic atrophy and viral replication in skeletal muscles, leading to speculation about the impact of botulinum toxin on the treatment of spasticity in this group.[10,11] The aim of this study is to investigate the effect of BoNT-A on the spasticity and motor performance of children with cerebral palsy related to Congenital Zika Syndrome (CZS).

Materials & Methods

Study Design and Participants

A prospective longitudinal observational study of 34 children between 24 and 38 months, diagnosed with CP secondary to CZS and with a medical indication for the use of BoNT-A for the reduction of spasticity was carried out between 2018 and 2019 at the Professor Edgard Santos University Hospital associated with the Federal University of Bahia. The study did not include a comparison group.

The defining diagnostic criteria for spastic CP used in this study was presence of non-progressive spasticity-associated motor deficit affecting functional capacity, and arising from a pre-, peri or post-natal brain injury that occurred prior to the age of two. The defining diagnostic criteria for CZS was based on the criteria used by França et al.[12] for the selection of highly probable cases: neuroimaging examination (computed tomography and/or MRI) suggestive of congenital infection (cerebral calcifications, ventricular enlargement or both) and negative tests for other congenital infections (cytomegalovirus, rubella, toxoplasmosis and syphilis). Children who met the

CONTACT Rita Lucena rcslucena@yahoo.com.br Universidade Federal da Bahia, Av. Reitor Miguel Calmon, S/N, Vale do Canela, Salvador, BA 40110-100, Brazil

following criteria were eligible to be screened for potential inclusion:[1] children born to mothers whose pregnancies occurred at the time of the ZIKV epidemic in Brazil (date of birth post June 2015);[2] children manifesting the above-mentioned criteria for probable CZS; and[3] children whose mothers exhibited a rash during pregnancy (to add weight to the possibility of ZIKV infection during pregnancy).

The inclusion criteria were[1] presumed or confirmed diagnosis of CP secondary to CZS;[2] presence of spasticity;[3] functional impairment;[4] medical recommendation for intramuscular injection of botulinum toxin; and[5] parental consent to participate in the study. We excluded participants who changed their treatment regimen (antiepileptic drugs) during the assessment period, since this could interfere with the outcome.

Treatment Aims

Assessment and treatment aims were established according to the *International Classification of Functioning, Health, and Disability* for children with CP[13] and included the three domains of 'body functions and structures,' 'activities' and 'participation.'

In addition, the degree of spasticity, broad motor skills and parent's perception of improvement or worsening was assessed before and after treatment. Prior to investigation, parents were duly informed about the expected effect of botulinum toxin based on the child's performance level.

Procedure

BoNT-A was administered as part of the participants' medical treatment, by consultant child neurology specialists according to the anatomical references described in the literature. Intramuscular injections in the spastic muscles were administered uni- or bi-laterally, at a maximum dose of 40 units/kg of BoNT-A (*Dysport – Abobotulinumtoxin A*). Each 500-unit vial was diluted with 2.5 ml of 0.9% sodium chloride, meaning that each 0.1 ml contained 20 units. Administration was performed 30 to 40 minutes after placement of 2.5% lidocaine and 2.5% prilocaine (EMLA) patches and after local asepsis with 2% chlorhexidine. The applications were performed only once on each child and no child in the study had previously undergone this procedure.

Outcome Assessment and Statistical Analysis

All children were assessed by an interdisciplinary team (physiotherapists, speech language therapists and child neurologists) prior to, and six weeks following, the administration of BoNT-A. The assessment stages were:

(1) Motor evaluation was performed according to the **Gross Motor Function Classification System (GMFCS)**, an instrument, which quantitatively assesses broad motor skills and provides functional categorization from I to V. Children classified as level I can walk at home, climb stairs without the use of a railing, and perform gross motor skills such as running and jumping with limited speed, coordination and balance. Children classified as level II can climb stairs holding onto a railing, but have difficulty walking long distances and balancing on uneven terrain. Children classified as level III can walk using a hand-held mobility device in most indoor settings, use wheeled mobility when traveling long distances, and may self-propel for shorter distances. Level IV is reserved for children that use methods of mobility requiring physical assistance or powered mobility in most settings. Children at level V are always transported in a manual wheelchair.[14,15]

(2) Muscle tone assessment scale (**Modified Ashworth Scale**). This is one of the most widely used instruments to characterize muscle tone, with six possible results (0, 1, 1+, 2, 3 and 4) that categorize increased degree of spasticity, with 0 being a patient with no increase in muscle tone and 4 a patient with the affected limb rigid in flexion or extension. In our study, category 1+ was recorded as 1.5 to facilitate statistical analysis.[16] This scale is validated for Brazilian Portuguese.[17]

(3) The **Patients' Global Impression of Improvement (PGI-I)**, which evaluates the parents' subjective perception of improvement in symptoms following intervention. This contains seven categories (1 to 7) – the lower the number, the better the result.[18,19]

The team's assessment prior to BoNT-A administration included analyzing the child's head circumference at birth and assessing weight, height and other anthropometric parameters.

To characterize the sample, we performed a descriptive statistical analysis of the data. The evaluation measures' adherence to the normality curve was determined by the Shapiro–Wilk test and histogram, plus a Skewness and Kurtosis analysis. Mean and standard deviations were used as central and dispersion tendency measures for variables with normal distribution. For variables with non-normal distribution, we used medians and the interquartile range. For a comparison of pre- and post-botulinum toxin measurements, we applied the Student's *t*-test or, when the data was not normally distributed, its nonparametric counterpart (Wilcoxon/Mann–Whitney). Correlation between variables was assessed by either the Pearson or Spearman correlation test, according to data normality. As a secondary analysis, to evaluate the clinical response predictors, we performed simple linear regression model analyses for the muscle groups in which more than 10 children received the BoNT-A application. We considered dependent variables to be the Patients' Global Impression of Improvement scale for the muscle group and variation in the MAS for the biceps brachii. In addition, we performed correlation analysis between the dependent variables (PGI-I and MAS) and covariables (selection based on clinical judgment) that could interfere with the outcome. The selected variables were age, weight, BoNT-A dose applied, number of primitive reflexes and head circumference growth delta. We used the STATA 14.0 statistical program for iOS and $p < .05$ values were considered statistically significant.

Ethical Aspects

The study was approved by the FIOCRUZ Research Ethics Committee (Consubstantiated Opinion no. 3.184.683) and is included in the research line under cooperation from this agency with the Medical School of Bahia at the Federal University of Bahia. The children were included in the study following written and verbal informed consent from their parents.

Results

Sample Characteristics

Between August and December 2018, 34 children (18 (53%) female and 16 (47%) male) with spasticity due to cerebral palsy as a secondary condition of CZS were subjected to BoNT-A administration. Sample characteristics are presented in Tables 1 and Tables 2. The age, weight, head circumference at birth and at time of assessment, and growth in head circumference were normally distributed. Age varied from 24 to 38 months (32.06 ± 3.07 months). Mean head circumference at birth was 29.64 cm (± 1.91 cm). Head circumference data at birth was missing in the medical record for two of the 34 participants. Mean head circumference at time of assessment was 41.25 cm (± 3.08 cm). Mean growth in head circumference since birth was 11.6 cm (± 3.12 cm). Participants' mean weight was 11.70 kg (± 2.18 kg).

Participant 16 alone presented with auditory impairment and arthrogryposis in the lower right limb, corresponding to 3% of the sample. Participant 27 presented with left hip dislocation and also represented 3% of the sample. All the children were involved in rehabilitation programs and all were accompanied by physiotherapists. Eighty-five percent were also accompanied by speech language therapists and 79% by occupational therapists. Most of the children presented limited functional performance. In the sample, only three children were able to sit without support before they had reached 2 years of age and these three did not present with epilepsy, visual or intellectual deficits, in contrast to the rest of the sample.

Primitive reflexes were present in 56% of the cases. The prevalence of children presenting only one of the primitive reflexes was 24%. Two of the reflexes were observed simultaneously in 9% of the sample, while three were present in 24%.

In relation to tone, each participant presented with spasticity in the lower limbs, while 94% and 91% presented with spasticity of the upper right and left limbs, respectively. The muscles most frequently selected for neuromuscular block were the adductor longus, biceps brachii, and triceps surae in 17 (50%), 12 (35%) and 6 (18%) subjects, respectively.

Outcome Assessment

Following treatment, parents reported reduction in muscle tone (100%), increased range of motion in lower (61.8%) and

Table 1. Clinical profile of the 34 participants with cerebral palsy secondary to CZS.

Participant	Age (months)	Sex	HC at birth (cm)	Current HC (cm)	Weight (kg)	Epilepsy	Visual impairment	Type of cerebral palsy
1	31	F	31	41	13	N	Y	SQ
2	32	M	31	41.2	10.3	N	N	SQ
3	27	F	28	39	10.4	Y	N	SQ
4	33	M	28	42	13	Y	Y	SQ
5	32	M	.	43	15	Y	N	SQ
6	36	M	29	37.5	12.7	Y	Y	SQ
7	24	M	32	45	10	N	N	SQ
8	32	M	31.5	42	10	Y	N	SQ
9	31	F	28	39	8.9	Y	N	SQ
10	32	F	28	36.5	10	Y	N	SQ
11	32	M	31.5	43	13	Y	N	SD
12	29	F	30.5	40.5	11.3	Y	Y	SQ
13	32	F	30.5	41.5	8.9	N	N	SQ
14	31	F	31	39	10.3	N	N	SQ
15	30	F	28	35.5	9.3	Y	Y	SQ
16	30	F	33	44	11.5	Y	Y	SQ + D
17	30	F	29.5	39.6	8	Y	N	SQ + D
18	29	M	31	42	12	Y	N	SQ
19	32	M	32	44.8	9.5	N	Y	SQ + D
20	29	F	28	41	13	N	Y	SQ
21	30	F	26	40	11.8	Y	Y	SQ
22	33	F	28	44	17.3	Y	Y	SQ
23	35	M	.	40	11.8	Y	Y	SQ
24	36	M	31.5	43.5	12	Y	Y	ST + D
25	38	F	30	32	14.5	Y	Y	SQ
26	35	F	29	38	11	N	N	SQ
27	37	F	27	40	10.8	Y	Y	SQ
28	37	M	27.5	43.5	16.6	N	N	SQ
29	29	M	32	43.5	13	Y	Y	SQ
30	34	M	27	47	10.5	Y	Y	SQ
31	31	M	29	43	11	N	N	SD
32	37	M	31	45	10	Y	N	SQ + D
33	32	F	32	44	12	Y	N	SM
34	32	F	27	40.5	15.3	Y	N	SQ

Note: F: female; M: male; N: no; Y: yes; SQ: spastic quadriplegia; SD: spastic diplegia; D: dyskinetic; ST: spastic triplegia; SM: spastic monoplegia.

Table 2. Frequency of motor characteristics of the 34 participants with cerebral palsy secondary to CZS.

Clinical features	Values (n/%)
URL Spasticity	32 (94)
ULL Spasticity	31 (91)
LRL Spasticity	34 (100)
LLL Spasticity	34 (100)
Orofacial dyskinesia	10 (29)
Moro Reflex	9 (26)
ATNR	17 (50)
STNR	12 (35)
APR	5 (15)
LPR	3 (9)
PPR	3 (9)
GMFCS I	0
GMFCS II	0
GMFCS III	3 (9)
GMFCS IV	2 (6)
GMFCS V	29 (85)

URL: upper right limb; ULL: upper left limb; LRL lower right limb; LLL: lower left limb; ATNR: Asymmetrical tonic neck reflex; STNR: Symmetrical tonic neck reflex; APR: Anterior Propping Reflex; LPR: Lateral Propping Reflex; PPR: Posterior Propping Reflex; GMFCS: Gross Motor Function Classification System.

Table 3. Results observed by parents following child treatment with BoNT-A.

Aspect observed	Values (%)
Reduced muscle tone	100
Increased range of motion in the lower limbs	61,8%
Increased range of motion in the upper limps	38,2%
Improved sitting mobility	14,7%
Maintenance of orthostatic posture	5,8%
Facilitated hygiene	44,1%
Improved posture to facilitate the use of orthoses	14,7%

upper (38.2%) limbs, facilitated hygiene (44.1%) and other outcomes, which are described in Table 3.

The children were reassessed on average 42 days following the first administration. One child began to walk without support 3 weeks following administration of BoNT-A in the triceps surae. Table 4 shows the results for the study's primary outcome. According to parental perceptions, 97.9% of them observed improvement in range of motion or reduction in spasticity of the muscle subject to blocking. When considering all the muscles, the PGI-I mode was rated as a 1 or very much improved. There was no record of deterioration following administration of the toxin. When participants' parents were asked about occurrence of adverse effects, none were reported.

Table 4. Patients' global impression of improvement scale according to location of toxin administration.

Muscles (number of children)	PGI-I scale						
	1	2	3	4	5	6	7
Biceps (12)	7	3	2	0	0	0	0
Triceps (6)	4	1	1	0	0	0	0
Deltoid (2)	2	0	0	0	0	0	0
Flexor carpi ulnaris (2)	2	0	0	0	0	0	0
Adductor longus (17)	10	4	3	0	0	0	0
Hamstrings (2)	1	1	0	0	0	0	0
Gastrocnemius (1)	1	0	0	0	0	0	0
Gastrocnemius + Soleus (5)	3	1	1	0	0	0	0
Total (47)	30	10	7	0	0	0	0
(%)	63.8	21.3	14.9	0	0	0	0

PGI-I: Patients' Global Impression of Improvement (1. Very much improved; 2. Much improved; 3. Minimally improved; 4. No change; 5. Minimally worse; 6. Much worse; 7. Very much worse).

We performed a Mann–Whitney test to compare MAS results pre- and post-BoNT-A, since the categorical data is non-binary. There was a statistically significant difference between the measurements (rank sum of MAS pre-BoNT-A = 111.5 and rank-sum of MAS post-BoNT-A = 59.5; $p = .0122$).

Correlations

BoNT-A was administered in the biceps of 12 participants, of whom nine were evaluated prior to and following the procedure (Table 5). We observed a negative correlation between the number of primitive reflexes (ATNR, STNR and Moro) and the dose administered in the biceps (−0.84/ $p = .0007$). Compared to the baseline, the median reduction in the MAS score following administration was 0.5 (IQR = 0).

We observed a statistically significant negative correlation between current weight and biceps PGI-I (−0.91/ $p = .0007$), in that the greater the weight, the lower the PGI-I score. The correlation observed between PGI-I and dose administered in the biceps was not statistically significant (0.07/ $p = .8504$).

We identified a weak and negative correlation between reduction in MAS (pre/post difference) and PGI-I score for the biceps, which was not statistically significant (−0.20/ $p = .6096$).

The positive correlation observed between the child's weight and the triceps PGI-I was not statistically significant (0.95/ $p = .0513$), as opposed to the corresponding score for the biceps PGI-I, which was negative and statistically significant. No correlation was found between these two variables for the adductor muscle.

Two participants were administered with BoNT-A in the flexor carpi ulnaris muscles, and also in the deltoid and hamstrings. Due to the small sample size of this subgroup, it was not possible to conduct correlation analysis.

Linear Regression

Simple linear regression was performed, taking as the dependent variables the PGI-I for the biceps brachii and the adductor, and the variation in MAS for the biceps brachii. Independent variables imputed to the model were age, sex, weight, head circumference growth delta, number of primitive

Table 5. Assessment of right biceps muscle tone before and after administration of botulinum toxin in nine participants and patients' global impression of improvement following the procedure.

Participant	Dose per muscle (units)	Modified Ashworth scale		PGI-I
		Before	After	
1 (P 8)	125	1	2	2
2 (P 10)	100	2	1.5	2
3 (P 11)	100	2	1.5	1
4 (P 13)	100	1.5	1	3
5 (P14)	125	2.0	1.5	1
6 (P15)	125	3.0	3.0	1
7 (P18)	100	3.0	1.5	1
8 (P 25)	190	1.5	1.5	1
9 (P 28)	200	2.0	1.5	1

P = Participant; PGI-I: Patients' Global Impression of Improvement (1. Very much improved; 2. Much improved; 3. Minimally improved; 4. No change; 5. Minimally worse; 6. Much worse; 7. Very much worse).

reflexes present, and total toxin dose by weight. Weight was the only predictor for the biceps brachii PGI-I ($p = .01$; coefficient: −0.20; constant: 4.09), in that the greater the weight, the lower the PGI-I score.

Discussion

The study assessed the spasticity response to BoNT-A in a cohort of 34 children with CP related to CZS. The majority of the parents (97.9%) reported improvement in range of motion or reduction in spasticity after their child received BoNT-A and no adverse effects were reported. To the best of our knowledge, there are no studies that assess the use of BoNT-A in this population. The findings of this study advance our knowledge of treatment of spastic CP in children with CZS by demonstrating the positive effects of BoNT-A, including functional improvements and reduced muscle tone.

The ZIKV epidemic in Brazil was accompanied by a substantial increase in cases of congenital microcephaly. Data regarding this cohort has recently been published and an analysis of the phenotype expression of the sample described so far, shows that most of the children suffering from brain injury have spastic quadriplegia cerebral palsy with early signs of poor motor prognosis, persistent primitive reflexes, absence of functional communication and significant cognitive delay.[4] According to parameters established by the WHO, 96.1% of children with CP related to CZS present gross motor skills at 2 years of age that are normally found in an infant of up to 4 months. Motor development curves in this same group, according to the GMFCS, demonstrate that children with quadriplegia have already obtained approximately 90% of their expected development potential.[20]

This study included children with CP, microcephaly and, except in five cases, GMFCS V. Rehabilitation presents significant challenges and botulinum toxin may be particularly relevant to this population in order to reduce spasticity, facilitate positioning, and improve both posture and range of motion. Spasticity is the main clinical consequence for children with CP and may cause pain, deformities, postural asymmetries and impede mobility, postural transfers, as well as gross and fine motor skills. For subjects with GMFCS IV and V, therapy also aims to facilitate hygiene, reduce pain and improve the quality of life of both the individuals and their families.[21]

The intramuscular administration of BoNT-A has been widely studied in children with CP. Inhibition of acetylcholine vesicle exocytosis in neuromuscular end plates causes functional denervation, prevents the neural activation of muscle fibers and leads to dose-dependent paresis and tone reduction.[22] A recent systematic review documented the safety and effectiveness of botulinum toxin for children with CP.[23] Although widely employed, few studies have attempted to determine the long-term impact of repeated injections. A study in rats demonstrated increased response to the stretch reflex following botulinum toxin injection, indicating that anomalous muscle fiber excitability could potentially increase after repeated injections. This information raises new questions about its potential long-term benefit, especially in children.[22]

The use of *Abobotulinumtoxin A* was due to it being made available via Brazil's Unified Health System's Exceptional Medicines Program and previous evidence about safety within the pediatric age range.[23,24] There is no uniform treatment strategy for BoNT-A in CP and best dosing practices have varied over the years. The total number of stipulated doses per unit per kilo of body weight is not evidence-based and relies on specialist expertise.[9] The per muscle toxin doses used by physicians were based on Brazilian guidelines,[25] i.e. they did not exceed the maximum dose of 40 units per kilo of weight and prioritized those muscle groups where spasticity had created the greatest functional impairment, according to both parent and physiotherapist. Previous studies of children with single and multiple doses have demonstrated good tolerability and efficacy, and self-limited and irrelevant adverse effects.[26] Possible side effects of BoNT-A include hematoma, local pain and weakness in adjacent muscles and, less frequently, muscles distant from the application site.[25]

The prognosis of CP has been the object of several investigations. A systematic review and meta-analysis demonstrated that factors relating to independent gait acquisition in children with cerebral palsy are sitting without support before reaching 2 years of age and the absence of epilepsy, visual impairment or intellectual disability.[27] A study by Vles et al. demonstrated a statistically significant improvement in the maintenance of orthostasis and gait following administration of botulinum toxin in children with spastic CP and severe motor dysfunction. This finding could also be observed in one participant in our study.[28]

The functional alterations reported in this study, such as greater facility in positioning the child, improved care and hygiene and improved gross motor function, have also been described in other studies that have assessed the effect of BoNT-A in children with spastic CP and GMFCS IV or V. Manzano et al. and Vles et al. demonstrated statistically significant improvements in the subjects' care.[28,29] Fragala et al. and Gooch and Sandell reported improvement in both child's positioning and subject care; however, they did not conduct a statistical analysis of this data due to limited sample size.[30,31] Certain studies have assessed the perception of subjects or their caregivers regarding improvements following BoNT-A administration. Three of these studies used descriptive measures to report perceived improvement following toxin use.[30,32,33] BoNT-A and other rehabilitation strategies for neurological disorders[34–38] could also improve quality of life and reduce the mental health burden inherent to certain chronic illnesses for patients and their carers.[39,40]

One of the main challenges to our study was the definition of parameters to assess muscle tone. The children presented severe functional impairment, with significant muscle hypertonia and intense reactivity to motor assessment maneuvers. More than half demonstrated persistent primitive reflexes, which are also negatively associated with motor prognosis, as seen in other studies.[41,42] In this study, in order to standardize data collection, an attempt was made to evaluate the spasticity of the biceps, adductor longus and hamstrings by analyzing muscle electrical activity through surface electromyography (EMG) in 10 children. We proposed to obtain parameters through the Hilbert–Huang transform[43]

according to EMG records made before, during, and after muscle stretching. However, we found that when this assessment was applied to children with CZS, there were complications for the optimal collection of EMG signals, such as interference from primitive reflexes and the already greatly increased basal tone. Goniometry was also considered as an outcome assessment parameter, but it did not prove to be accurate, with wide intra-individual variation in tone and range of motion in assessments repeated at five-minute intervals, even when performed under the same conditions (temperature and positioning of the child). We therefore opted to use MAS, a widely used resource in similar studies. However, it should be noted that its reliability and reproducibility have been called into question and there has been evidence of clinimetric inconsistencies, as also seen with the Tardieu scale.[44,45] The PGI-I provided additional elements for a subjective analysis of the outcome, inferring that the toxin has an impact on functionality, which appears to be more clinically relevant than the objective muscle tone measurements. In other words, a reduction in tone in a specific muscle group following botulinum toxin did not, in isolation, determine the efficacy of the treatment, except when this was accompanied by a clinically relevant positive result, with a corresponding impact on the quality of life of the child and their family. The perception of improvement might be the best clinical indicator of response to the toxin in this population, given the severe motor impairment and low prospect of improvement.

The low variation in response to the stretching stimulus by obtaining an EMG signal reinforced the possibility of trophic changes in the muscle that led to shortening. However, BoNT-A was effective in promoting functional improvement and changes to muscle tone according to the PGI-I and MAS, respectively, in children with CZS that had impaired functional levels and extensive brain injury. This was also observed with other causes of cerebral palsy.[21] The challenges inherent in intra- and inter-rater variations in measuring spasticity highlight the need for researchers to develop other tools for objective tone assessment that can be accurately employed in children with severe motor impairment.

Conclusion

Although BoNT-A proved to be effective in promoting functional improvements and reducing muscle tone in children with CP as a secondary condition of CZS, possible muscle changes related to the early infection of this condition may promote a different response from that observed in individuals with CP due to other causes. There are many gaps regarding the influence of botulinum toxin on prognosis, in particular in relation to prevention or delay of the appearance of joint deformities and hip dislocation. Although this study had limitations, we believe that its approach and findings contribute to a better understanding of the treatment of spasticity and its potential complications in children with CZS.

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Disclosure statement

There is no conflict of interest.

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References

1. Lyra PPR, Campos GS, Bandeira ID, Sardi SI, Costa LFDM, Santos FR, Ribeiro C, Jardim A, Santiago A, de Oliveira P, et al. Congenital Chikungunya virus infection after an outbreak in Salvador, Bahia, Brazil. Am J Perinatol Rep. 2016;6(03):299–300. doi:10.1055/s-0036-1587323.
2. Siddique R, Liu Y, Nabi G, Sajjad W, Xue M, Khan S. Zika Virus potentiates the development of neurological defects and microcephaly: challenges and control strategies. Front Neurol. 2019;10:(April):1–9. doi:10.3389/fneur.2019.00319.
3. Musso D, Gluber DJ. Zika Virus. Clin Microbiol Reviews. 2016;29:487–524.
4. Carvalho A, Brites C, Mochida G, Ventura P, Fernandes A, Lage ML, Taguchi T, Brandi I, Silva A, Franceschi G, et al. Clinical and neurodevelopmental features in children with cerebral palsy and probable congenital Zika. Brain Dev. 2019;41(7):587-594. doi: 10.1016/j.braindev.2019.03.005.
5. Singhi P, Ray M. Botulinum toxin in children with cerebral palsy. Indian J Pediatr. 2004;71(12):1087–91. doi:10.1007/BF02829820.
6. Hsiung GYR, Das SK, Ranawaya R, Lafontaine AL, Suchowersky O. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. Mov Disord. 2002;17(6):1288–93. doi:10.1002/mds.10252.
7. Sales HF, Cerqueira C, Vaz D, Medeiros-Rios D, Armani-Franceschi G, Lucena PH, Sternberg C, Nóbrega AC, Luz C, Fonseca D, et al. The impact of botulinum toxin type A in the treatment of drooling in children with cerebral palsy secondary to Congenital Zika Syndrome: an observational study. Neurol Res. 2021;43(1):54-60. doi: 10.1080/01616412.2020.1820698.
8. Bandeira ID, Jagersbacher JG, Barretto TL, Santos CV, Lucena R. Botulinum toxin type A in the treatment of facial myotonia in Schwartz-Jampel syndrome. Muscle and Nerve. 2017;56:2.
9. Strobl W, Theologis T, Brunner R, Kocer S, Viehweger E, Pascual-Pascual I, Placzek R.. Best clinical practice in botulinum toxin treatment for children with cerebral palsy. Toxins (Basel). 2015;7(5):1629–48. doi:10.3390/toxins7051629.
10. Chan JF, Yip CC, Tsang JO, Tee KM, Cai JP, Chik KK, Zhu Z, Chan CC, Choi GK, Sridhar S, et al. Differential cell line susceptibility to the emerging Zika virus: implications for disease pathogenesis, non-vector-borne human transmission and animal reservoirs. Emerg Microbes Infect. 2016;5(8):e93. doi: 10.1038/emi.2016.99.
11. Chimelli L, Melo ASO, Avvad E, Wiley CA, Camacho AHS, Lopes VS, Machado HN, Andrade CV, Dock DCA, Moreira ME, et al. The spectrum of neuropathological changes associated with congenital Zika virus infection. Acta Neuropathol. 2017;133(6):983–99. doi:10.1007/s00401-017-1699-5.
12. Franca GVA, Schuler-Faccini L, Oliveira WK, Henriques CMP, Carmo EH, Pedi VD, Nunes ML, Castro MC, Serruya S, Silveira MF, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete

investigation. Lancet (London, England). 2016 Aug;388 (10047):891–97. doi:10.1016/S0140-6736(16)30902-3.
13. World Health Organization: international classification of functioning, disability and health (ICF). World Heal Organ. 2001.
14. Palisano R, Rosenbaum P, Walter S, Russel D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39:214–23. doi:10.1111/j.1469-8749.1997.tb07414.x.
15. Hiratuka E, Matsukura TS, Pfeifer LI. Adaptação transcultural para o Brasil do sistema de classificação da função motora grossa (GMFCS). Rev Bras Fisioter. 2010;14(6):537–44. doi:10.1590/S1413-35552010000600013.
16. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67 (2):206–07. doi:10.1093/ptj/67.2.206.
17. Texeira LF, Olney SJ, Brouwer B. Mecanismos e Medidas de Espasticidade.pdf. Rev Fisioter. 1998;5:4–19.
18. Andrade AC, Magnavita GM, Allegro JVBN, Neto CEBP, Lucena RDCS, Fregni F. Feasibility of transcranial direct current stimulation use in children aged 5 to 12 years. J Child Neurol. 2014 Oct;29(10):1360–65. doi:10.1177/0883073813503710.
19. Bandeira ID, Guimarães RS, Jagersbacher JG, Barretto TL, de Jesus-Silva JR, Santos SN, Argollo N, Lucena R. Transcranial Direct Current Stimulation in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (ADHD): A Pilot Study. J Child Neurol. 2016 Jun;31(7):918–24. doi:10.1177/0883073816630083
20. A Ventura P, C Lage ML, L de Carvalho A, S Fernandes A, B Taguchi T, Nascimento-Carvalho CM. Early Gross Motor Development Among Brazilian Children with Microcephaly Born Right After Zika Virus Infection Outbreak. J Dev Behav Pediatr. 2020;41(2):134-140. doi: 10.1097/DBP.0000000000000722.
21. Pin TW, Elmasry J, Lewis J. Efficacy of botulinum toxin A in children with cerebral palsy in gross motor function classification system levels IV and V: a systematic review. Dev Med Child Neurol. 2012;55(4):304–13. doi: 10.1111/j.1469-8749.2012.04438.x.
22. Pingel J, Hultborn H, Näslund-Koch L, Jensen DB, Wienecke J, Nielsen JB. Muscle disuse caused by botulinum toxin injection leads to increased central gain of the stretch reflex in the rat. J Neurophysiol. 2017;118(4):1962–69. doi:10.1152/jn.00276.2017.
23. Guyot P, Kalyvas C, Mamane C, Danchenko N. Botulinum Toxins Type A (Bont-A) in the management of lower limb spasticity in children: a systematic literature review and Bayesian network meta-analysis. J Child Neurol. 2019;34(7):371–81. doi:10.1177/0883073819830579.
24. Bandeira ID, Mendoza J. Medical education and leadership: a call to action for Brazil's mental health system. Int J Med Educ. 2018 Jun 22;9:170-172.doi:10.5116/ijme.5b1b.b0a2
25. Dorf SR, Caldas CACT, Chueire RHMF, Carvalho JH, Brito JAF, Maciel SC, Sarmento EM, Ramos AM. Uso prático da AbobotulinumtoxinA no tratamento de espasticidade em crianças com paralisia cerebral. Acta Fisiátrica. 2018;24(3):160–64. doi:10.5935/0104-7795.20170030.
26. Matthews D, Camba GC, Pascual-Pascual I, Tilton AH, Gormley M, Mahmood A, Picaut P, Snyder D, Delgado MR. Poster 485 safety and tolerability of abobotulinumtoxinA (dysport) in children (2-17 years) with lower limb spasticity due to cerebral palsy: a pooled analysis of 8 clinical trials. Pm&R. 2016;8(9):S318. doi:10.1016/j.pmrj.2016.07.403.
27. Keeratisiroj O, Thawinchai N, Buntragulpoontawee M, Siritaratiwat W. Derivation of an ambulatory prognostic score chart for Thai children with cerebral palsy aged 2 to 18. J Med Assoc Thail. 2016;99:1298–305.
28. Vles GF, de Louw AJA, Speth LA, van Rhijn LW, Janssen-Potten YJM, Hendriksen JG, Vles JSH. Visual analogue scale to score the effects of botulinum toxin A treatment in children with cerebral palsy in daily clinical practice. Eur J Paediatr Neurol. 2008;12 (3):231–38. doi:10.1016/j.ejpn.2007.08.002.
29. Manzano FS, Granero LM, Masiero D, Dos SMTBR. Treatment of muscle spasticity in patients with cerebral palsy using BTX-A: a pilot study. Spec Care Dent. 2004;24(4):235–39. doi:10.1111/j.1754-4505.2004.tb01699.x.
30. Fragala M, O'neil M, Russo K, Dumas H. Impairment, disability, and satisfaction outcomes after lower-extremity botulinum toxin a injections for children with cerebral palsy. Pediatr Phys Ther. 2002;14:132–44.
31. Gooch JL, Sandell TV. Botulinum toxin for spasticity and athetosis in children with cerebral palsy. Arch Phys Med Rehabil. 1996;77 (5):508–11. doi:10.1016/S0003-9993(96)90042-8.
32. Lundy CT, Doherty GM, Fairhurst CB. Botulinum toxin type A injections can be an effective treatment for pain in children with hip spasms and cerebral palsy. Dev Med Child Neurol. 2009;51(9):705–10. doi:10.1111/j.1469-8749.2009.03315.x.
33. Fattal-Valevski A, Giladi N, Domanievitz D, Zuk L, Masterman R, Harel S, Wientroub S, Hayek S. Parameters for predicting favorable responses to botulinum toxin in children with cerebral palsy. J Child Neurol. 2002;17(4):272–77. doi:10.1177/088307380201700407.
34. Bandeira ID, Lins-Silva DH, Barouh JL, Faria-Guimarães D, Dorea-Bandeira I, Souza LS, Alves GS, Brunoni AR, Nitsche M, Fregni F, et al. Neuroplasticity and non-invasive brain stimulation in the developing brain. Prog Brain Res. 2021;264:57-89. doi: 10.1016/bs.pbr.2021.04.003.
35. Barretto TL, Bandeira ID, Jagersbacher JG, Barretto BL, de Oliveira E Torres ÂFS, Peña N, Miranda JGV, Lucena R. Transcranial direct current stimulation in the treatment of cerebellar ataxia: A two-phase, double-blind, auto-matched, pilot study. Clin Neurol Neurosurg. 2019 Jul;182:123-129.doi:10.1016/j.clineuro.2019.05.009
36. Rios DM, Correia Rios M, Bandeira ID, Queiros Campbell F, de Carvalho Vaz D, Lucena R. Impact of Transcranial Direct Current Stimulation on Reading Skills of Children and Adolescents With Dyslexia. Child Neurol Open. 2018 Oct 4;5:2329048X18798255. doi: 10.1177/2329048X18798255.
37. Guimarães RSQ, Bandeira ID, Barretto BL, Barretto TL, Wanke T, Alves COC. The effects of transcranial direct current stimulation on attention and inhibitory control of children and adolescents with attention-deficit/hyperactivity disorder (ADHD): study protocol for a randomized, sham-controlled, triple-blind, cross-over trial. Medicine (Baltimore). 2021 Feb;100(8):e24283. doi:10.1097/MD.0000000000024283.
38. León Ruiz M, Rodríguez Sarasa ML, Sanjuán Rodríguez L, Benito-León J, García-Albea Ristol E, Arce Arce S. Current evidence on transcranial magnetic stimulation and its potential usefulness in post-stroke neurorehabilitation: opening new doors to the treatment of cerebrovascular disease. Neurologia. 2018 Sep;33 (7):459–72. doi:10.1016/j.nrl.2016.03.008.
39. Barreto TM, Bento MN, Barreto TM, Jagersbacher JG, Jones NS, Lucena R, Bandeira ID. Prevalence of depression, anxiety, and substance-related disorders in parents of children with cerebral palsy: a systematic review. Dev Med Child Neurol. 2020;62 (2):163–68. doi:10.1111/dmcn.14321.
40. Silva-Moraes MH, Bispo-Torres AC, Barouh JL, Lucena PH, Armani-Franceschi G, Dorea-Bandeira I, Vieira F, Miranda-Scippa Â, Quarantini LC, Lucena R, Bandeira ID. Suicidal behavior in individuals with amyotrophic lateral sclerosis: A systematic review. J Affect Disord. 2020;277:688-696. doi: 10.1016/j.jad.2020.08.066.
41. Bleck EE. Locomotor prognosis in cerebral palsy. Dev Med Child Neurol. 1975;17(1):18–25. doi:10.1111/j.1469-8749.1975.tb04952.x.

42. Molnar G, Gordon S. Cerebral palsy: predictive value of selected clinical signs for early prognostication of motor function. Arch Phys Med Rehabil. 1976;57(4):153–58.
43. Hu B, Zhang X, Mu J, Wu M, Wang Y. Spasticity assessment based on the Hilbert-Huang transform marginal spectrum entropy and the root mean square of surface electromyography signals: a preliminary study. Biomed Eng Online. 2018 Feb;17(1):27. doi:10.1186/s12938-018-0460-1.
44. Mutlu A, Livanelioglu A, Gunel MK. Reliability of Ashworth and modified Ashworth scales in children with spastic cerebral palsy. BMC Musculoskelet Disord. 2008;9(1):1–8. doi:10.1186/1471-2474-9-44.
45. Ka Ling Yam W, So Mei Leung M, Alice Ho Miu P. Interrater reliability of modified Ashworth scale and modified Tardieu scale in children with spastic cerebral palsy from the departments of paediatrics and adolescent medicine (Dr Yam). J Child Neurol. 2006;21(12):1031–35. doi:10.1177/7010.2006.00222.