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Effectiveness of Botulinum Toxin A First Injection on Gastrocnemius Muscle Spasticity in Children with Cerebral Palsy: Clinical and Elastosonography Study

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Abstract

Background: An accurate assessment of the spasticity in the spastic forms of cerebral palsy (CP) is important to establish the effectiveness of therapeutic management. The modified Ashworth scale (MAS) is the most frequently used method in the assessment of spasticity in clinical practice. However, this method does not allow an objective, precise and reliable assessment because of the lack of standardization and the low level of reliability. Elastosonography (ES) is an imaging method that assesses the viscoelastic characteristics of tissues non-invasively. **Aim:** The aim of this study was to assess the stiffness of gastrocnemius muscle (GCM) in children with spastic CP by ES and to investigate the sonoelastographic changes and its correlations with clinical evaluation parameters (MAS) after botulinum toxin type A (BTA) injections. **Methods:** This prospective, analytical and diagnostic study involved children with spastic CP receiving a first injection of BTA to GCM. Muscle stiffness was measured with MAS and ES before the procedure, and at 1, 2, 3, 4 weeks, 3 and 6 months post-injection. ES parameter [Strain Index Value (SIV)] and MAS scores before and after the treatment were compared. **Results:** Fifteen children with spastic CP were enrolled in the study. The mean age was 6.8 years ± 3.85 and the mean body weight was 21.4 kg ± 7.8. Abobotulinum toxin A (Dysport®) injections were administered to 5 children (33.3%) with an average dose of 180 ± 179.44 units and Onabotulinum toxin A (Botox®) injections were administered to 10 children (66.7%) with an average dose of 63 ± 27.51 units in GCM. The average MAS score was 2.5 and SIV was measured as 2.38 ± 0.57 before BTA. At 2 weeks after BTA injection, significant

improvements were observed in MAS grades and SIV ($p < 0.05$). These statistically significant improvements persisted for up to 3 months for the MA score and only 2 months for the SIV. Positive significant correlations were observed between the SIV and the MAS score at different times of the evaluation. **Conclusion:** The results of this study suggest that ES is a promising diagnostic tool allowing the assessment of the viscoelasticity of spastic muscles in real time as it was described in the spasticity stretch reflex.

Subject Areas

Clinical Medicine, Pharmacology

Keywords

Cerebral Palsy, Muscle Spasticity, Elastosonography, Botulinum Toxins, Type A

1. Introduction

In cerebral palsy (CP), spasticity is the main motor disorder, observed in approximately 85% of children [1], and the most common source of motor impairment [2]. Thus the therapeutic objective in children with spastic CP is to reduce spasticity, and prevent retractions and the resulting functional loss [3] [4]. Many therapeutic strategies are used to improve functional status in children with spastic CP, with pharmacological, rehabilitative and surgical means [5]. Botulinum toxin type A (BTA) is a drug widely used in children with CP [1] [6]. It has been used for over 25 years in the management of pediatric lower and upper limb hypertonia. The most common indication is the injection of the triceps surae muscle for the correction of spastic equinus gait in children with cerebral palsy [6]. In clinical practice, several scales are used to assess spasticity. MAS has been used clinically to examine the efficacy of the treatment of spasticity [7]. Measurements of spasticity using the MAS have acceptable intrarater reliability but poor interrater reliability [7] [8].

In order to contribute to the right therapeutic choice, it is important to accurately assess the effectiveness of medical and rehabilitation treatment as well as the progression of the spasticity in children with CP.

The architectural characteristics of muscles can be evaluated by ultrasound, thus helping to understand the mechanisms of spasticity. Elastosonography (ES), a recent imaging technique, provides information about muscle elasticity and allows qualitative and quantitative measurements of the mechanical properties of muscle tissue [9].

In children with CP, the evaluation of spastic muscles by ES is recent and studies are still scarce, but the authors concluded that it is useful in combination with clinical means [10] [11] [12] [13]. However, no study to date has compared very early and long-term ES changes in children with CP after a first injection of

BTA.

The aim of this study was to assess the spasticity of the gastrocnemius muscle (GCM) of children with CP using ES, to follow the evolution of spasticity of the GCM after a first injection of BTA and to investigate a correlation between the ES measurements and the MAS at the different stages of the evaluation.

2. Methods

2.1. Study Design

This was a prospective, analytical and a diagnostic test evaluation study conducted between September 2020 and January 2022.

2.2. Patients

Children with spastic CP treated in the department of Physical Medicine and Rehabilitation (PMR) at the University Hospital of Monastir were assessed for eligibility.

Children's parents were informed about the study and provided written consents. All procedures of the study were approved by the ethical committee of the Faculty of Medicine of Monastir under the number IORG 0009738 No. 16/OMB 0990-0279.

The inclusion criteria were as follows:

- Age between 2 and 15 years
- Spastic CP
- A muscle spasticity score more than 1 according to the MAS
- Independent ambulation with or without gait-assistive devices
- Patients who will receive a first injection of BTA (Abobotulinum toxin A or Onabotulinum toxin A) in the GCM

Exclusion criteria were as follows:

- Previous BTA injection in the GCM
- Previous lower extremity surgery
- Presence of fixed ankle contracture

Information about the children was obtained from the corresponding doctor. Systematically, and after parental consent, the children included in the study received a schedule to ensure follow-up at the different times of the assessment (before the injection and 1, 2, 3, 4 week and 3 and 6-month post-injection).

2.3. Assessment Procedure and Data Collection

The collection of socio-demographic and clinical data was carried out on pre-established forms filled out at each consultation according to the predefined schedule.

Clinical and functional evaluations were performed by the same physician.

The evaluation form included:

- Identification of the child: file number, telephone number, name, first name, age, sex, weight and height.

- Clinical form of CP based on the classification of the SCPE group (Surveillance of Cerebral Palsy in Europe) [14].
- Evaluation of the functional level by Gross Motor Function-Classification System (GMFCS) [15], Gillette score [16] and the gait pattern.
- Injection characteristics: type of toxin, number of muscles injected, dose of toxin injected into the GCM and total dose injected per session.
- Monitoring table for the assessment of spasticity by the clinical parameters and ES.

In our study, spasticity in GCM was clinically assessed by the MAS after 30 minutes of rest.

The following parameters were noted:

- The dorsiflexion angle with the knee straight and the knee flexed passively
- The flexum of the knee present spontaneously

2.4. Quantitative Assessment of Motor Function by Gross Motor Function Classification System (GMFCS) and Gillette Score

The severity of motor impairment was determined by the GMFCS [15]. It is a validated reference tool, recognized by the international scientific community in children with CP and classifying the impairment into five levels of severity [17].

Gillette score is a descriptive scale of walking corresponding to part of the Gillette Functional Assessment Questionnaire (FAQ) [16]. It is a self-administered questionnaire used by authors since 1994 for children assessed in the gait laboratory at Gillette Hospital. It has ten levels (from level 1 for the most dependent children to level 10 for the most independent) which assess the subject's usual walking abilities indoors and outdoors.

2.5. Gait Pattern

The type of gait pattern was determined according to that established by Rodda and Graham [5] [18]. It is a classification of walking patterns in a sagittal plane considering the whole pelvis, hips, knees, ankles and by introducing a notion of scalability.

2.6. Caracteristics of Botulinum Toxin Injection

The toxin injection data were noted:

- Type: Abobotulinum toxin A or Onabotulinum toxin A
- Injected dose into the GCM (in Allegran unit for Onabotulinumtoxin A and in Speywood unit for Abobotulinumtoxin A)

The injected dose per muscle and per session was calculated per kg of body weight.

The initial dose of Abobotulinum toxin A (Dysport®) recommended in the summary of product characteristics (SPC) is 20 Speywood Units/Kg to be distributed between the two legs for diplegics, 10 Speywood Units/Kg in the affected leg for hemiplegics and 5 Speywood Units/Kg/chief muscle of the GCM in

the event of injection of only GCM [19]. The initial dose of Onabotulinumtoxin A (Botox®) recommended in the SPC is 4 Allergan Units/Kg injected into the affected limb in case of hemiplegia and 6 Allergan Units/Kg to be distributed between the two legs concerned for diplegics [20].

During the injection session the child was installed in prone position, the knee was if possible in slight flexion thanks to the installation of a cylindrical wedge under the ankle which eliminates any support of the dorsal aspect of the foot. The two chiefs were approached posteriorly, and the BTA injections were performed perpendicular to the skin planes, at the level of areas rich in motor plates or motor points [21] and at slightly different heights. These areas rich in motor plates were assessed as a percentage of an average leg length measured from the tibial malleolus (TM) to the medial joint line of the knee (MJLK):

- The medial chief: a hand's width below the joint line of the knee, about 3/4 of the MT-MJLK.
- The lateral chief: 2 - 3 cm higher, about 4/5 of the TM-MJLK.

2.7. Elastosonographic Evaluation of Spasticity

Strain ES assessment was carried out in the imaging department of Fattouma-Bourguiba Hospital in Monastir. All measurements were performed by the same radiologist who had 15 years of experience in musculoskeletal imaging.

All the children were scanned on an examination table in the prone position with their feet hanging off the edge to prevent muscle contraction.

The examination was performed on a device (LOGIC E9, GE Healthcare, Milwaukee, WI, USA) using a multifrequency linear transducer (4 - 15 MHz). Each medial and lateral GCM was assessed with a transducer placed perpendicular to the axis of the muscle with minimal compression (**Figure 1**).

The measurements were made at the motor points of each medial and the lateral GCM.

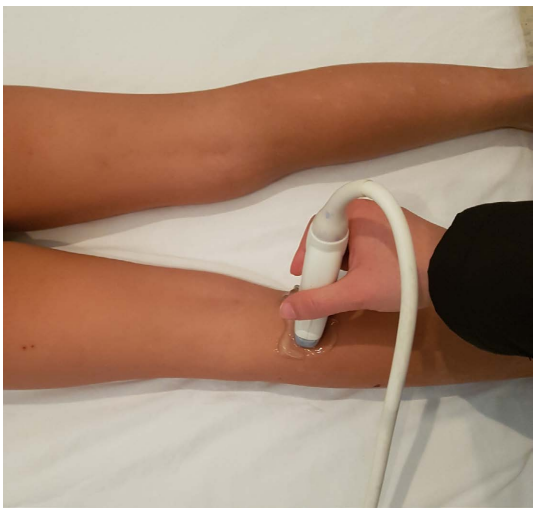

Figure 1. Placement of the transducer on the gastrocnemius muscle.

The Strain index value (SIV) was calculated comparing the GCM (A) to the subcutaneous adipose tissue (B) (SIV = (B/A). Three measurements of the SIV were taken for each medial and lateral GCM then the average of the three measurements was calculated (Figure 2).

2.8. Statistical Analysis

The statistical analysis was performed using IBM® Statistical Package for the Social Sciences software version 18.0.For statistical purposes, a score of 1 using the MAS was considered as 1, while a score of 1+ was regarded as 2 and so on up to a score of 4, which was regarded as 5 [22]. To compare the means, the student's T test was used. The Pearson correlation coefficient was used in the study of the correlation between the strain ES values [Strain Index Values (SIV)] and the MAS scores before and after the treatment and between the parameters of evaluation of GCM spasticity, whether clinical (MAS) or radiological (SIV) on the one hand, and motor function assessment parameters (GMFCS and Gillette score) on the other hand. p value < 0.05 was considered statistically significant.

3. Results

Between September 2020 and January 2022, 15 children were enrolled in the study. The mean age was 6.8 ± 3.85 years (6 girls and 9 boys). Of the children with CP, seven had hemiplegia, four triplegia and four had diplegia or quadriplegia (Table 1).

Abobotulinum toxin A injections were administered to 5 children with an average dose of 180 units and Onabotulinum toxin A injections were administered to 10 children with an average dose of 63 units in GCM.

The mean MAS score of the GCM after 1, 2, 3, 4 weeks and 3 months after intervention decreased significantly from the pretreatment scores (p < 0.01) (Table 2).

For the GCM, two weeks after BTA injection, the mean SIV was 1.95 ± 0.43 and this improvement was considered statistically significant (p = 0.01). The mean SIV was 1.94 ± 0.56 after 3 weeks and 1.79 ± 0.66 after 4 weeks with a significant p (p < 0.05) (Table 2).

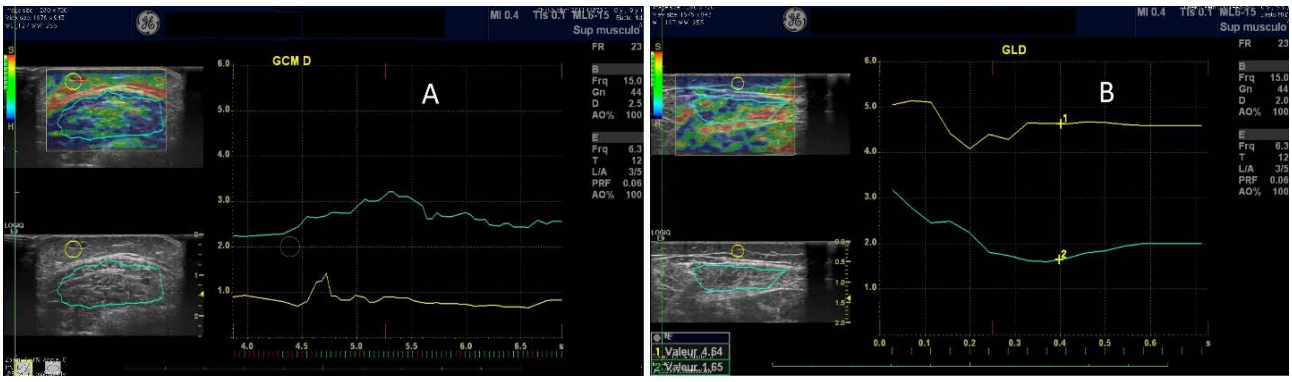

Figure 2. Sonoelastographic images of medial gastrocnemius muscle (A) and lateral gastrocnemius muscle (B).

Table 1. Demographic and clinical characteristics of the study group.

Demographic and clinical parameters	Patients (n = 15)
Age (years)	6.8 ± 3.85
Gender (female/male) (n)	6/9
CP type (n) (%)	
Hemiplegic	7 (68%)
Triplegic	4 (16%)
Quadriplegic	2 (8%)
Diplegic	2 (8%)
Weight (Kg)	
GMFCS level (n) (%)	
I	1 (6.67%)
II	9 (60%)
III	3 (20%)
IV	2 (13.33%)
Gillette score (n) (%)	
2	1 (6.67%)
6	4 (26.66%)
7	8 (55.33%)
8	1 (6.67%)
9	1 (6.67%)
Type of gait pattern (n) (%)	
Type of gait pattern for diplegics n = 8:	
True equinus	2 (25%)
Jump gait	5 (62.5%)
Crouch gait	1 (12.5%)
Type of gait pattern for hemiplegics n = 7:	
True equinus	3 (42.86%)
Jump knee	2 (28.57%)
Flexion adduction et intern rotation of the hip	2 (28.57%)

CP: cerebral palsy, GMFCS: Gross Motor Function Classification System.

A statically significant positive correlation was found between MAS scores and GMFCS levels ($p = 0.04$ and $r = 0.86$). The more the spasticity increases, the more the GMFCS level increases. The correlation between MAS scores and Gillette scores was negative and statistically significant ($p = 0.03$ and $r = -0.65$). The more spasticity increases, the more the Gillette score decreases (Table 3).

Table 2. Evolution of Modified Ashworth Scale score and strain index value of the gastrocnemius muscle at the different evaluation times.

Time	MAS of GCM	P (Between pre-injection and the different times of the evaluation)	Strain Index Value of GCM	P (Between pre-injection and the different times of the evaluation)
Pre-injection	2.57 ± 1.07		2.15 ± 0.41	
W1	2.21 ± 1.18	**0.05**	2.11 ± 0.62	0.64
W2	2 ± 1	**0.02**	1.95 ± 0.43	**0.01**
W3	1.77 ± 1.21	**0.005**	1.94 ± 0.56	**0.03**
W4	1.68 ± 1.41	**0.003**	1.79 ± 0.66	**0.04**
M3	1.84 ± 1.34	**0.015**	1.95 ± 0.79	0.07
M6	2.38 ± 1.03	0.45	2.14 ± 0.63	0.87

MAS: Modified ashworth scale, SAV: Strain index value, GCM: gastrocnemius muscle, W1: one week after the injection, W2: two weeks after the injection, W3: three weeks after the injection, W4: four weeks after the injection, M3: three months after the injection, M6: six months after the injection.

Table 3. Correlation study between modified Ashworth score, GMFCS and Gillette score before the injection.

	MAS of GCM
GMFCS 2.4 ± 0.82	2.57 ± 1.07 **p = 0.04** **r = 0.86**
Gillette score 6.92 ± 1.95	2.57 ± 1.07 **p = 0.03** **r = −0.65**

GMFCS: Gross Motor Function-Classification System; GCM: gastrocnemius muscle.

The correlation study between the radiological evaluation parameter of spasticity (SIV) and the evaluation parameters of motor function is detailed in Table 4. A statically significant positive correlation was found between SIV and GMFCS levels ($p = 0.04$ and $r = 0.5$). The more the spasticity increases, the more the GMFCS increases.

The correlation between SIV and Gillette score was negative and statistically significant ($p = 0.03$ and $r = -0.57$). The more spasticity increases, the more the Gillette score decreases.

A statistically significant positive correlation between SIV and MAS of GCM was found at different times of assessment. The SIV was strongly correlated with the MAS in pre-injection and after 2 and 4 weeks with $r > 0.6$ and $p < 0.05$ (Table 5).

4. Discussion

Nineteen spastic lower limbs were evaluated clinically (MAS) and radiologically

Table 4. Correlation study between the strain index value, Gross Motor Function Classification System and Gillette score before the injection.

	SIV
GMFCS **2.4 ± 0.82**	2.24 ± 0.49 **p = 0.04** **r = 0.5**
Gillette score **6.92 ± 1.95**	2.24 ± 0.49 **p = 0.03** **r = −0.57**

SIV: Strain index value; GMFCS: Gross Motor Function-Classification System.

Table 5. Correlation study between Strain Index Value and modified Ashworth score.

Time	Pre-injection	W1	W2	W3	W4	W3	W6
MAS	2.57 ± 1.07	2.2 ± 1.18	1.64 ± 0.93	1.77 ± 1.21	1.68 ± 1.41	1.84 ± 1.34	2.38 ± 1.03
SIV	2.15 ± 0.41	2.11 ± 0.62	1.95 ± 0.43	1.94 ± 0.56	1.79 ± 0.66	1.95 ± 0.79	2.14 ± 0.63
R	0.86	0.45	0.62	0.57	0.64	0.54	0.45
P	0.04	0.05	0.02	0.01	0.04	0.03	0.05

AM: Ashworth modifié; SIV: Strain index value; W1: one week after the injection, W2: two weeks after the injection, W3: three weeks after the injection, W4: four weeks after the injection, M3: three months after the injection, M6: six months after the injection.

(ES). The mean MAS score initially was 2.57 ± 1.07. The mean SIV of GMC was 2.15 ± 0.41 before BTA injection. In the literature, we found a single study using the ES in a quasi-static method by measuring the SIV of the spastic biceps brachii muscle in hemiplegic adults with a stroke [23]. The mean MAS score was 3.58 ± 0.57 and the mean SIV value was 2.83 ± 1.38 before BTA injection. In our study, for a MAS score of 2.57, the mean SIV value was lower at 2.15.

Studies evaluating GCM spasticity in children with CP have mostly used dynamic ES [10] [11] [24] [25].

Our study is the first to evaluate the spasticity of the GCM in children with CP at close intervals after a first BTA injection at 1, 2 and 3 weeks. Indeed, a close evaluation over time allows a close assessment of the time of onset of the effect of BTA in children with CP, still imprecise in the literature [26] [27].

Clinically, the improvement in the MAS score for the GCM was considered significant ($p < 0.05$) between D0 (before BTA injection) and W2 and very significant ($p < 0.01$) between D0 and W3 and between D0 and W4. Thus, based on the MAS score, the effect of BTA in our study population begins to appear at W2 after injection of BTA and this statistically significant improvement persists for up to 3 months.

In ES, the improvement of SIV was statistically significant between D0 and W2, D0 and W3, and D0 and W4. The effect of BTA on GCM spasticity appears in ES at W2 as clinically. However, this effect persists up to W4 only.

Askin *et al*. [23], using the strain ES, evaluated the spasticity of the biceps brachii muscle in 48 hemiplegic patients with a stroke before BTA injection and after 4 weeks. In this study, the improvement in MAS score as well as SIV was statistically significant after 4 weeks of BTA injection.

These elastosonographic results are comparable to our study as the SIV values decreased (less than 2) after BTA injection.

In children with CP, the elastosonographic parameters measured to assess spasticity are different. Park and Kwon [12], to assess GCM spasticity in 17 children with spastic CP, used the quasi-static elastosonographic method (real-time sonoelastography (RTS)). They noted a significant decrease in MAS score, red pixel intensity and score (RTS) after 4 weeks of BTA injection which are indicators of decreased muscle spasticity.

Using the same method, Won-Yub Lee *et al*. [25] conducted a study on 16 children with spastic CP and found an improvement in the MAS score as well as the RPI (Red pixel intensity) score after 1, 3 and 6 months of the BTA injection. The improvement in the RPI score was statistically significant for up to six months after BTA injection. The doses of BTA used were higher than the doses injected in our study. This method used in these two studies is comparable to our method and the results are similar with an evolution towards a decrease in the SIV.

In our study, the improvement in the MAS score was statistically significant between W2 and M3 while the improvement in SIV was statistically significant only between W2 and W4. The doses used in our study for GCM were between 30 and 100U Allergran for Onabotulinum toxin A and 80 to 500U Speywood for Abobotulinum toxin A.

Few studies in the literature reported the duration of the effect of BTA, but the data that exist are comparable to ours: according to recent system reviews [26] [27], the effect of BTA persisted up to 4 to 12 weeks. Only one study evaluated the effect of BTA with ES at 6 months in children with CP [25]. In this study, the improvement in elastosonographic parameters persisted for up to 6 months. Note that the doses of BTA used in this study are higher than the doses used in our study (6 U/Kg of Onabotulinum toxin A against 4 U/Kg in our study).

Regarding the duration of improvement in spasticity on the clinical and elastosonographic plan, it nevertheless seems interesting to wonder about the results obtained in our study on spasticity at M3, which seemed less good by the elastosonographic study. One possible explanation is that, the injections were in a big muscle, and the doses injected were low, resulting in a decrease in the duration of the expected effect. In our study, a statically significant positive correlation was found between MAS score and GMFCS and between SIV and GMFCS. A statistically significant negative correlation was also found between MAS score and Gillette score and between SIV and Gillette score. The more spasticity increases, the more motor function is impaired. Park *et al*. [12] assessed the spasticity of children with CP using ES by measuring RTS score and motor function

by the Gross Motor Function Measure (GMFM). The authors did not find a correlation between the RTS score and the GMFM score. They explained these results by the fact that the majority of the children had a very impaired GMFM.

In our study, the correlation between SIV and MAS score was statistically significant at different times of assessment. These results are consistent with the literature and several studies have found a correlation between the MAS and elastosonographic parameters [10] [12] [23] [24] [28]. Indeed, Askin *et al*. [23] had found a positive significant correlation between the MAS and the SIV of the biceps brachii muscle in hemiplegic adults with stroke. In the study of Park and Kwon [12], the MAS of GCM in children with CP was positively correlated with the elastosonographic parameter (RTS) ($r = 0.778$ and $p < 0.05$).

The main limitations of our study are the following:

- The number of children included in our study was 15 children collected over a period of 16 months. A larger sample would allow a better analytical study with more significant results.
- A comparative evaluation between the healthy limb and the spastic limb could not be carried out since most of the children were diplegic.
- Although widely used, the MAS does not provide an accurate and objective assessment of spasticity. In our study, we opted for this scale to be able to compare our results with the literature.
- The ES used makes it possible to theoretically estimate the Young's modulus by applying a continuous constraint. However, the latter being unknown (operator-dependent), we usually only represent the deformation whose final image; "Strain image" which offers only a qualitative measure, incapable of giving a quantified image in kilo-Pascal of the local Young's modulus.

5. Conclusion

This study demonstrated significant durable reduction of gastrocnemius muscle spasticity after the first injection of BTA in children with cerebral palsy. SIV was correlated with the MAS score at different times of the evaluation. ES seems to be a promising diagnostic tool that facilitates the assessment of tissue spasticity.

Conflicts of Interest

The authors declare no conflicts of interest.

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