Original Article

Evaluation of the Results of Botulinum Toxin Injection in Children with Cerebral Palsy Aged between 2 and 15 years, using Two Techniques: Electrostimulation and Ultrasound

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Abstract

Objective: The objective of our study is to compare ultrasound and electrostimulator guidance for the injection of diluted botulinum neurotoxin Type A. **Materials and Methods:** Eighty-six children were injected under a pacemaker and 94 under ultrasound. The injection involved the muscles of the lower limbs in 180 children aged between 2 and 15 years. Assessment was by the Modified Ashworth Scale, lower-limb range of motion, and Gross Motor Function Classification System (GMFCS) for function, as well as procedural pain. **Results:** The analysis does not find any difference between the two techniques concerning spasticity, functional evolution according to the GMFCS, and articular amplitudes, with the exception of the popliteal angle of the right knee with an estimated $P = 0.01$ for the group injected under ultrasound. Interventional pain between the two groups found a significant difference ($P = 0.04$) in favor of ultrasound identification. **Conclusion:** The stimulator had the same results as ultrasound on the orthopedic level of spasticity as well as on gross motor function. Nevertheless, ultrasound tracking remains more comfortable and less painful than stimulator tracking.

Keywords: Botulinum toxin A, cerebral palsy, electrostimulator, spasticity, ultrasound

Introduction

Cerebral palsy (CP) is a set of movement and/or posture and motor function disorders.[1,2] It can present itself in different clinical forms, depending on the overall topography, with quadriplegia, diplegia, triplegia, and hemiplegia being the most common. Furthermore, on the neurological symptomatology level, CP can be pure spastic, dystonic, athetotic, or mixed. This symptomatology may be associated with cognitive impairment.[3,4] The clinical picture may also be accompanied by other deficient signs, which may be sensory, somatic, or psycho-intellectual, causing an additional handicap. Concerning the etiology of this impairment, any lesion affecting the growing brain, either intrauterine or during childbirth or during the first 2 years of life, can be the cause of CP.[5]

Admittedly, the cerebral lesion is stable and permanent, but certain abnormalities that it generates evolve over time.[6-8] Primary abnormalities, directly related to brain damage (poor selective motor control, muscle tone disorder, or spasticity),[9] lead to the appearance of secondary abnormalities (orthopedic deformities and locomotion disorder). The tertiary abnormalities appear, in the course of evolution, in order to compensate for the secondary deformations and the functional disorders.[10-12]

The management of CP is multidisciplinary, and physical medicine and rehabilitation represent the pivot of this management, based essentially on the prevention of secondary disorders during the period of growth.[13]

The treatment of spasticity responds to a fairly wide therapeutic arsenal[14] that can be administered locally or systemically,[15,16]

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depending on the clinical examination and the treatment objectives.[17,18] botulinum Toxin A (BoNTA) currently represents one of the best local treatments.[19-22]

Since its advent, several tracking methods have been used for its administration.[23,24]

The objective of our study is to find the existence, or not, of a difference in effectiveness between ultrasound guidance and electrostimulator in guided BoNTA administration and doing so by comparing their effect on the muscles of the lower limbs in children with CP (walking or with walking potential).

Materials and Methods

Patients

TThis is a prospective observational study comparison between two groups of CP patients treated with BoNTA for the muscles of the lower limbs, the first group injected under an electrical stimulator comprising 86 patients, and the second under ultrasound with 94 patients. We used botulinum toxin Type A 500 U at a dilution of 2.5 ml. The dose used was weight dependent and did not exceed 20 U/kg for the bilateral forms and 10 U/kg for the unilateral ones. With regard to ultrasound identification, we used, of course, high-frequency linear probes (higher than 7.5).

This study was carried out in the Physical Medicine and Rehabilitation Department of the Douéra University Hospital from September 2017 to December 2020. The study included all children with CP, aged between 2 and 15 years, presented with standing and/or walking potential, as well as previously injected children with an injection delay exceeding 6 months. The noninclusion criteria concerned spasticity secondary to a pathology other than CP and bedridden children without any motor acquisition.

Data collected

All patients included in the first consultation received BoNTA injections during the second consultation. The third early checkup consultation was held 1 month after injection which allowed for an initial clinical assessment with development of the specific treatment protocol for each patient. This care includes a series of stretching casts, physiotherapy sessions as well as therapeutic education sessions for parents. A final consultation is carried out between 3 and 6 months after the injection in order to identify the clinical parameters of follow-up and to judge the effectiveness of the overall treatment.

The comparison of the two techniques was carried out by comparing spasticity according to the Modified Ashworth Scale (MAS),[25] the orthopedic assessment of the lower limbs (abduction flap, popliteal angle, and Silver_skiold test),[26] as well as functional progression global scale according to the Gross Motor Function Classification System (GMFCS) Scale[27] and the Visual Analog Pain Scale (VAS) for procedural pain.[28]

Statistics

Data entry and analysis were performed with Statistical Package for the Social Sciences Chicago, Illinois, USA. The data were described statistically for the entire population and according to the identification technique (stimulator or ultrasound). Paired quantitative data were compared before and after injections using Wilcoxon tests. Unpaired qualitative data were analyzed using Chi-square test. Statistical tests were two-sided and results were significant at the 5% level. During the analysis, some variables were created or transformed.

Ethics

The study was approved by the Scientific Council of the Faculty of Medicine of the University of Saad Dahleb Blida, and it is in accordance with the Declaration of Helsinki.[29]

Results

Population and disease characteristics

For the topographic form of CP, we find a predominance of the diplegic form estimated at 96 (i.e., 53.3%), followed by the quadriplegic form with a frequency of 54 (30%), and for the form overall, we find 83.3% of bilateral forms and 16.7% of unilateral forms. All GMFCS levels are found in our analysis, with a predominance of levels with a good functional prognosis (i.e., 1.2 and 3). All patients have spasticity, with a frequency of 72.2% for pure spastic forms, but there are also mixed forms, with the presence of cerebellar syndrome in 7.2% of cases and dystonia in 23.3% of cases. The presence of cognitive disorders is found in 27.2% of cases [Table 1].

Therapeutic characteristics

Our patients benefited during the treatment period from an average number of 3 injections by specifying that we inject an average of 3.86 ± 1.28 muscles, with extremes of 1–6 muscles per session [Table 2].

The most toxined muscles are the gastrocnemius with a frequency of 65.6%, followed by the gracilis which was injected in 53.9% of the cases, the hamstrings injected in 39.4%, and the soleus which was injected in 26.7% of cases.

The average duration of follow-up for our patients is 3.5 years, with a minimum of 1 year and a maximum of 13 years [Table 2].

91.1% of our patients benefited from physiotherapy sessions, while 8.9% did not [Table 2].

56.1% of our patients walk without a technical aid, compared to 26.1% using the walking frame [Table 2].

For upper-limb orthosis, the correct positioning splint was prescribed in 45 of our patients (i.e., 25% of cases), while the lower-limb brace was prescribed in nearly 80% of cases with a prescription for walking orthosis alone in 5.6% of cases, posture orthotics in 20.6% of cases, and both orthotics in 55% of cases [Table 2].

Table 1: Characteristics of the sample

Characteristic	Effective (%)			*P*
	Global (180; 100%)	Under stim (86; 47.8%)	Under ultrasound (94; 52.2%)	
The topographic form				
Diplegia	96 (53.3)	42 (48.83)	54 (57.44)	0.48
Tétraplégia	30 (16.7)	29 (33.72)	25 (26.59)	
Hemiplegia	54 (30)	15 (17.44)	15 (15.95)	
The overall shape				
Unilateral	30 (16.7)	15 (17.44)	15 (15.95)	0.84
Bilateral	150 (83.3)	71 (82.55)	79 (84.04)	
The GMFCS classification				
Level 1	27 (15)	9 (10.46)	18 (19.14)	0.01
Level 2	58 (32.2)	21 (24.41)	37 (39.36)	
Level 3	44 (24.4)	30 (34.88)	14 (14.89)	
Level 4	24 (13.3)	13 (15.11)	11 (11.70)	
Level 5	27 (15)	13 (15.11)	14 (14.89)	
Functional prognosis				
Good prognosis	129 (71.7)	60 (69.76)	69 (73.40)	0.62
Average prognosis	51 (28.3)	26 (30.23)	25 (26.59)	
Associated clinical signs				
Cerebellar syndrome	13 (7.2)	10 (11.6)	3 (3.2)	0.04
Dystonia	42 (23.3)	19 (22.1)	23 (24.5)	0.72
Cognitive disorders	49 (27.2)	32 (37.2)	17 (18.16)	0.005
Age, mean±SD	5.46±3.36	5.53±2.98	5.73±3.48	0.47
Spasticity, mean±SD	2.42±0.69	2.42±0.69	2.53±0.56	0.22
Sex (male/female)	82/98 Ratio=1, 19	38/48 Ratio=0, 79	60/34 Ratio=1, 7	0.01

SD: Standard deviation, GMFCS: Gross Motor Function Classification System

Table 2: Therapeutic characteristics of the subjects included

Characteristic (*n*=180)	Effective (%), mean±SD
Number of toxin injections	3.38±2.91
Number of muscles injected	3.86±1.28
Physiotherapy	
No	16 (8.9)
At our level	19 (10.6)
Other structure	96 (53.3)
At our level + other structure	49 (27.2)
Technical assistance for walking	
None	101 (56.3)
Walker	61 (33.6)
Walking sticks	3 (1.7)
Wheelchair	15 (8.4)
Lower-limb orthosis	
None	34 (18.9)
Lower-limb orthosis	10 (5.6)
Posture brace	37 (20.5)
Lower-limb orthosis + posture brace	99 (55)
Upper-limb orthosis	45 (25)

SD: Standard deviation

Effect of the toxin on the general population

The average spasticity according to MAS was 2.48 ± 0.62 before BoNTA injection, increased to 2.01 ± 0.66 after injection. We note that BoNTA is effective in improving spasticity with a very significant *P*. The analysis of the evolution of the articular amplitudes before and after injection of BoNTA finds a clinical improvement of all the amplitudes. The gain in terms of degrees is 3.36° for the abduction flap, 2° for the right popliteal angle, 1.9° for the left popliteal angle, 4.23° for the right Dorsiflexion stretched knee (DFSK), 4.16° for the left DFSK, 4.2° for the right DFFK, and 4.81° for the right DFFK [Table 3]. The study of the functional evolution according to the GMFCS and the overall estimate of the degree of functional prognosis shows an improvement after the injection of BoNTA with a very significant P, and in other words, the injection of BoNTA improved the overall function of the general population [Table 3].

Evaluation of the therapeutic objective

The analysis of the evolution of spasticity in the two groups was done by calculating the average before and after the injection of BoNTA. The comparison of the two means did not find any difference between the two techniques, with 2.07 ± 0.68 for the first group and 1.95 ± 0.64 for the second group.

The comparison of joint amplitudes shows no difference between the two techniques, except for the popliteal angle of the right knee with $P = 0.01$, and a difference in gain of more than 6° for the group injected under ultrasound [Table 4].

Table 3: Botulinum toxin clinical efficacy criteria on enrolled subjects

Characteristic (n=180)	Mean±SD		P*
	Before toxin (n=86)	After toxin (n=94)	
Spasticity	248±62	201±66	$<10^{-3}$
Joint mobility			
Abduction flap	96.08±17.52	99.44±17.11	$<10^{-3}$
Right popliteal angle	35.41±15.36	37.41±16.22	$<10^{-3}$
Left popliteal angle	35.24±15.61	37.14±16.04	$<10^{-3}$
Right DFSK	3.59±11.31	7.82±9.36	$<10^{-3}$
Left DFSK	4.58±11.51	8.74±9.01	$<10^{-3}$
Right DFFK	13.37±13.08	17.57±10.52	$<10^{-3}$
Left DFFK	13.88±13.14	18.69±11.0	$<10^{-3}$
GMFCS			
Level 1	27±15	30±16.7	$<10^{-3}$
Level 2	58±32.3	80±44.4	
Level 3	44±24.4	44±24.4	
Level 4	24±13.3	16±8.9	
Level 5	27±15	10±5.6	
Functional prognosis			
Good prognosis	129±71.7	154±85.6	$<10^{-3}$
Average prognosis	51±28.3	26±14.4	

*P: Paired-sample t-test. DFSK: Dorsiflexion stretched knee, DFFK: Dorsiflexion flexed knee, SD: Standard deviation, GMFCS: Gross Motor Function Classification System

Table 4: Botulinum toxin clinical efficacy criteria on enrolled subjects

Characteristic	Mean±SD		P
	Under stim	Under ultrasound	
Spasticity	2.07±0.68	1.95±0.64	0.21
Abduction flap	98.14±15.70	100.64±18.32	0.329
Right popliteal angle	34.20±15.51	40.35±16.38	0.011
Left popliteal angle	35.58±15.47	38.56±16.50	0.214
Right DFSK	7.22±8.00	8.36±10.47	0.41
Left DFSK	8.19±8.86	9.26±9.16	0.427
Right DFFK	16.81±10.08	18.26±10.92	0.360
Left DFFK	18.88±11.59	18.51±10.65	0.822

DFSK: Dorsiflexion stretched knee, DFFK: Dorsiflexion flexed knee, SD: Standard deviation

The comparison of the functional evolution in the two groups finds a better improvement in the group injected under ultrasound, with a significant difference. Therefore, it can be concluded that the injection of BoNTA under ultrasound improved the overall function of brain-damaged children 56 times better than the children injected under stim [Table 5].

Using the VAS for assessment of pain during injection, the average pain in the overall sample was 6.52 ± 1.90. The comparison of the two groups found a clearly significant difference between the two techniques, with an estimated P = 0.04. The injection under ultrasound would be less painful than injection under stim and improves the child's comfort [Table 6]. It is important to emphasize that the injection is done after premedication with paracetamol and local anesthetic before the injection session associated with anxiolytics depending on the case. Paracetamol is given orally at a dose of 60 mg/kg, with a local anesthetic in the form of a cream.

Discussion

The effectiveness of BoNTA in the treatment of lower-limb spasticity has been the subject of several studies which have proven its beneficial effect on bothersome spasticity,[30-33] and our results are consistent with those found in previous studies. Regarding the comparison of the two tracking techniques, the research was very poor and was limited to the systematic review (Chan *et al*., 2019),[34] which cited the studies of Picelli *et al.* (2019, 2019). This team had compared the two techniques in hemiplegic adults:

In 2012, they had compared the two techniques on the flexor muscles of the wrist and the fingers; they had objectified no difference between the two techniques in the treatment of the spasticity of the muscles of the hand nor on the improvement of the articular amplitudes.

In 2016, they compared the two techniques on the gastrocnemius in the lower limb, their conclusion was in favor of ultrasound, which would be more effective than the stimulator, on spasticity of the gastrocnemius (MAS and Tardieu score), and on the articular amplitudes of the ankle.

Our results show no difference between the two injection techniques in the improvement of spasticity according to MAS, with an average of 2.07 ± 0.68 for the first group and 1.95 ± 0.64 for the second group (P = 0.21). The injection of the toxin is done intramuscularly. An identical observation was made on the articular amplitudes of the ankle and hips

are to be considered. Nevertheless, our analysis revealed a significant discrepancy Improve the popliteal angle of the right knee by injecting the hamstring muscle under ultrasound with a needle ,the probability of occurrence is estimated at 0.01. These results need to be verified with a larger sample and randomization to increase the power of the study.

The systematic review (Chan *et al*., 2019)[34] and, more specifically, Simpson *et al*. had published updated practice guidelines for the American Academy of Neurology, where they concluded that comparative studies of three guiding techniques (manual, electrical stimulation, and ultrasound) favored no technique. Although there is consensus that ultrasound guidance provides the greatest anatomical accuracy for BoNTA injections, further trials are needed to determine whether it is superior to other guidance techniques when used alone. In this review, the studies by Picelli *et al*.[34] did not measure the impact of the spotting technique on functional outcomes, so the clinical relevance remains unknown.

The systematic review[35] concluded that spotting techniques (echo, electrostim, and EMG electromyogram) improved the accuracy of BoNTA injection, but it was more difficult to determine whether this would have improved clinical and functional results, however, the use of ultrasound is strongly recommended but requires specific training and equipment.

For our series, we observed an identical overall locomotor progression in the two groups without any difference. This is consistent with the results of spasticity and joint amplitude.

In addition to the effectiveness of BoNTA, procedural pain has raised a lot of questions, as BoNTA treatment is parenteral, and multi-site, inflicting pain on the child and even the family. In the absence of adequate analgesic preparation, the injection of toxin remains a painful and traumatic treatment, badly experienced by the child and his family.

The study by Mottu-Bayon, 2013,[36] had compared the pain according to the spotting technique during intramuscular injections of BoNTA in children. It had been concluded that ultrasound spotting was less painful than spotting under electrostimulation, with VAS means estimated at 2.7 ± 2.0 for ultrasound and 4.5 ± 3.2 for electrostimulation. There is a significant statistical difference in favor of the group injected under ultrasound compared to the other group ($P < 0.05$), despite the use of analgesics.[36]

The study by Charane, 2018,[37] found an average VAS under pacemaker in its overall sample, equal to 7.40 ± 2.35, which corresponds to intense pain. To conclude, the method of injection under electrical tracking remains a very painful method for children, especially in the absence of adequate analgesia.[37]

Our results agree with the data cited above, concluding that injection under ultrasound is less painful than injection under stimulator. The comparative results show a significant difference ($P = 0.04$) with a mean VAS estimated at 6.84 ± 1.99 for the first group and 6.23 ± 1.78 for the second group. It is important to specify that the Charane team used the same analgesic adjuvants, unlike the Mottu-Bayon team which also uses meopa is a french abreviation, in english we call it EMONO (equimolar mixture of oxygene and nitrous oxide).

Conclusion

Through our study, we were able to observe that botulinum toxin is effective in the management of spasticity of the lower limbs in CP, with an improvement in joint amplitude, the spasticity score, as well as the global functional evaluation. That being said, this efficacy is greater and better maintained when it is associated with adjuvant treatment and good integration of the parents in the care of their children. However, it is desirable to continue monitoring and management so as not to lose the benefit of this therapy, especially during the growth period.

We were also able to conclude that the effect of toxin in the management of spasticity of the lower limbs in brain-damaged patients is not related to the identification technique. On the spasticity level, on the orthopedic level, as well as on the global motor function, the stimulator had the same results as ultrasound. Despite this, ultrasound remains a method better appreciated by the manipulator given the anatomical precision that it offers him and the possibility of injecting deep, fine, and layered muscles.

Table 5: Botulinum toxin clinical efficacy criteria on

Characteristic ($n=180$)	Technical		*P*
	Under stim ($n=86$), *n* (%)	Under ultrasound ($n=94$), *n* (%)	
GMFCS			
Level 1	11 (12.79)	19 (20.21)	0.62
Level 2	39 (45.34)	41 (43.36)	
Level 3	24 (27.9)	20 (21.27)	
Level 4	8 (9.3)	8 (8.51)	
Level 5	4 (4.6)	6 (6.38)	
Functional prognosis			
Good prognosis	74 (86.04)	80 (85.10)	0.51
Average prognosis	12 (13.95)	14 (14.89)	

GMFCS: Gross Motor Function Classification System

Table 6: Comparison of pain between the two spotting techniques

	Global population ($n=180$)	Under stim ($n=86$)	Under ultrasound ($n=94$)	*P*
VAS, (mean±SD)	6.52±1.90	6.84±1.99	6.23±1.78	0.04

VAS: Visual Analog Scale, SD: Standard deviation

It is essential to also underline the preference raised by most parents of patients for ultrasound, as it is more comfortable for children and less painful, especially in the absence of adequate analgesia in the country.

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Conflicts of interest

There are no conflicts of interest.

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