

USE AND ADVERSE EFFECTS OF BOTULINUM TOXIN IN MANAGEMENT OF CHILDREN WITH SPASTIC CEREBRAL PALSY

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Abstract

Botulinum toxin is an important element in the therapeutic arsenal used in the treatment of spastic cerebral palsy. Blocking the neuromuscular plate allows spasticity removal in the involved muscle groups and facilitates the physical-therapy treatment. The paper highlights the main therapeutic indications of the botulinum toxin and its adverse reactions in treating children with spastic cerebral palsy. The adverse effects of the toxin, both local and general, are not linked to the orthopaedic use, occurring regardless of the pathology. Even though adverse effects are scarce they must be known in order to prevent additional and costly treatments. A study on 1872 patients was conducted over a period of 12 years. Effects of botulinum toxin were assessed at the first, second and third use. For each patient no more than three doses were used. The use of botulinum toxin is very effective in treating spastic cerebral palsy in children if the injection criterion is respected along with the technical principles. Adverse effects are minimal and do not pose the problem of applying additional therapies.

Rezumat

Utilizarea toxinei botulinice reprezintă un element important al arsenalului terapeutic la bolnavul spastic. Prin blocarea plăcii neuromusculare se permite înlăturarea spasticității grupelor musculare afectate și se asigură un tratament kinetoterapic mult mai eficient. Lucrarea elaborată încearcă să sintetizeze principalele indicații ale utilizării toxinei botulinice la pacienții spastici și, de asemenea, să atragă atenția asupra principalelor efecte adverse ale acestui tratament. Efectele adverse ale utilizării toxinei botulinice atât generale, cât și locale nu sunt specifice patologiei ortopedice, ele putând fi întâlnite ori de câte ori toxina botulinică este folosită, indiferent de patologia tratată. Cu toate că efectele adverse nu sunt importante (de cele mai multe ori sunt minore și spontan reversibile) ele trebuie cunoscute pentru a putea fi identificate și a preveni aplicarea unui tratament suplimentar costisitor și ineficient. Au fost luați în studiu un număr de 1872 de pacienți, pe o perioadă de 12 ani. Au fost studiate efectele toxinei botulinice atât la prima injectare, precum și la a doua și a treia injectare. La nici un pacient nu au fost depășite 3 injecții. În concluzie, utilizarea toxinei botulinice este o metodă eficientă de tratament a bolnavului spastic dacă sunt respectate criteriile de administrare injectională și principiile tehnice de realizare a acestora. Reacțiile adverse sunt minime și nu impun aplicarea nici unei metode suplimentare de tratament.

Keywords: botulinum toxin, adverse effects, children, cerebral palsy

Introduction

Spastic cerebral palsy (CP) in children is a relatively frequent condition in Romania, with an increasing incidence, mainly due to perinatal causes (cerebral hypoxia, prematurity, new-born nuclear jaundice), but any other central motor neuron and extrapyramidal path lesion can be incriminated [17]. Chronic infant encephalopathy or cerebral palsy (CP), as the World Health Organisation defines it, has peripheral manifestation by increasing the muscle tone, mainly of the flexors, thus different degrees of spasticity appears. With the progression of the disease, the spastic muscle groups create vicious positions. In early stages these positions can be corrected by methods that cancel spasticity but in advanced stages they can only be corrected with surgery [25].

In the first stage of spasticity (without muscle retraction) surgical treatment is inefficient, even harmful, creating severe muscle imbalance. Along the years, several methods have been used in diminishing spasticity (casting, alcohol infiltrations or neurectomies) but none of them was as efficient as botulinum toxin [1, 7, 21].

Botulinum toxin has eight major serotypes: A, B, C, D, E, F, G, H. Four are widely used in practice, three are serotype A: onabotulinumtoxin A, abobotulinumtoxin A, incobotulinumtoxin A and one is serotype B, rimabotulinumtoxin B [3, 4].

Injected in the spastic-muscle groups, the toxin is distributed selectively to the neuromuscular plates, blocking the discharge of acetylcholine. The absence of acetylcholine discharge blocks the nervous impulse transmission with lowering and even disappearance

of the muscle group spasticity [11]. Botulinum toxin cannot cure spastic cerebral palsy but through its actions, along with adequate physical therapy it can prevent sequelae and vicious positions. During the relaxation period that the toxin offers, the child can learn the walking scheme and gain the ability of managing fine movements and even though the spasticity reappears (the relaxing effect lasts between 4 and 6 months) the child learns how to manage it [3]. Another major advantage of this treatment is that it can postpone surgical treatment which is rarely followed by good results [1, 7, 21]. Two randomized studies have shown that botulinum toxin A improves initial foot contact and gross motor function [11, 15, 24].

During the phase of muscle retractions, the efficacy of the toxin treatment diminishes significantly and the vicious position can only be corrected by surgery. Despite all of this, whenever there is an exaggerated muscle tone, botulinum toxin can be used to increase the patient's quality of life.

An important part of our study was dedicated to analysing adverse effects of the toxin, assuring that this therapeutic method is a key element in the arsenal used to treat the spastic child. The literature data suggests that the adverse effects of the toxin are not linked to the affection for which it is used and they can arise regardless of the site of injection. We have monitored the occurrence of two adverse effect categories: local ones and general [1, 7, 21].

Materials and Methods

We present a prospective, observational study on a group of 1872 patients in a period of 12 years (2004 - 2016). The study was approved by the Ethics Committee of our institution. The patients were enrolled, after their parents/legal tutors, signed the informed consent. The inclusion criteria were: patients that suffered from CP, spastic and dyskinetic forms treated with Botulinum toxin Type A.

We have excluded the patients under 2 years of age, as for this age group there are no established injection protocols, excessive and premature spastic muscle groups that underwent lengthening for which relaxing through blocking the neuromuscular plates wouldn't bring any benefit.

The main objective of this study was to analyse the local and general effects in the Botulinum toxin treatment of CP patients and also assessing the efficacy of this therapy. The statistical data analysis was done by using Microsoft Office Excel.

Botulinum toxin type A was used (a protein complex with a molecular weight of 140,000 Dalton) giving it great neuromuscular plate penetration. Its origin lies among the seven neurotoxins produced by the anaerobe bacteria *Clostridium botulinum*. The injection blocks the release of acetylcholine from synaptic

vesicles. The neuromuscular plates cease their activity and after a while acetylcholine stops being released. According to most authors, muscle contracture reappears after new lower activity neuromuscular plates form at the site of injection [5, 9, 20, 23].

We used Botulinum toxin (Dysport[®], Ipsen) under lyophilized form of 500 IU. Each unit is the equivalent of LD50 (the lethal dose in 50% of the intra-peritoneal injected mice) [19].

The mean dose used was 20 - 30 IU/kg, the toxic dose being 500 times bigger than the therapeutic dose [18, 20, 23]. The use of a lower dose was avoided in order to prevent the lack of effect.

In order to quantify the injected dose we used the protocol from the Recovery Clinic in Besancon, France, dissolving the 500 IU in 2.5 mL of saline, obtaining a dilution of 200 IU/mL. We recommend to avoid stirring when dissolving the lyophilized toxin to prevent the loss of the characteristics of the toxin. The prepared solution is then aspirated in 1 mL syringes and injected under general anaesthesia in order to place multiple injections in the targeted spots. The total dose varies with the patient's weight and the muscle groups to be injected. The literature data shows that the repartition of the neuromuscular plates is not uniform and in order to inject the areas with a high density of neuromuscular plates we used electromyography [6, 25]. In the absence of electromyography, the map of neuromuscular points of Tardieu can be used [5, 7, 8, 9].

Eun Sook Park *et al.* used ultrasonography to demonstrate that Botulinum toxin A injections change muscle architecture. Spasticity was reduced when measured by Tardieu and Ashworth scale at 1 and 3 months after injection [10].

After injection we applied the international standard [18, 20, 23] for the disposal of botulinum toxin: the used vials, the syringes and needles to be introduced in a chloride hypertonic solution to inactivate the toxin; gloves and surgical drapes to be sent to the hospital's crematorium; the unused toxin not to be stored in vials and decontaminated using chloride solution for a 30 minute contact time and disposed of, down the drain, with plenty of water.

Results and Discussion

The majority, 76.3%, 1430 patients, belonged to the group of 2 to 7 years. Patients who were older than 17, represented a particular group, the toxin being injected for improving their condition in order to perform a mandatory surgical intervention (Figure 1). In most cases the total dose was of 500 IU, but because the quantity that has to be injected depends on the patient's weight and the targeted muscle groups, the dosage varied between 200 and 800 IU.

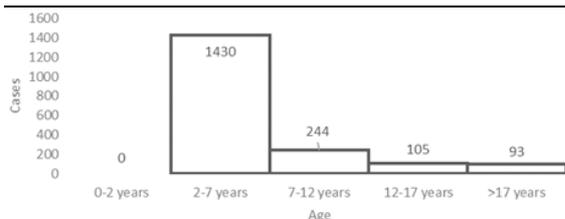


Figure 1.
Case repartition by age

Botulinum toxin indications

Absolute indications for injecting botulinum toxin. CP, especially the spastic and dyskinetic forms, where muscle retraction has not been installed.

Relative indications for injecting botulinum toxin. The spastic disease in which the muscle retraction has not set in, but in which the decrease of muscular hypertonia could lead to a motricity sector within normal range. Patients with spasticity that underwent surgery and don't have a big discrepancy between the sector of mobility and motricity after a possible length overcorrection.

Contraindications for injecting botulinum toxin. Patients with known hypersensitivity to any botulinum toxin preparation or to any of the excipients. Patients with infection at the sites to be injected or in patients known to be allergic to lactose.

Throughout our series 65% of the patients had absolute indication and 35% relative indication for toxin injection. From the cases with relative indications 29% had mild or moderate muscle retraction and 6% were operated prior to injection (Figure 2).

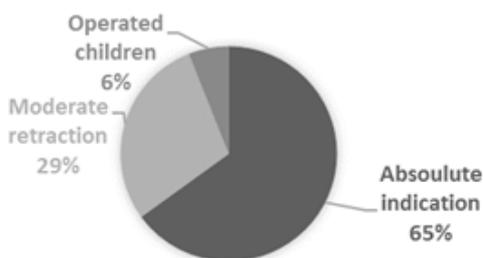


Figure 2.
Relative and absolute injection indications

The most frequent vicious position that was addressed was equinus foot, followed by *genu flexum* (Figure 3).

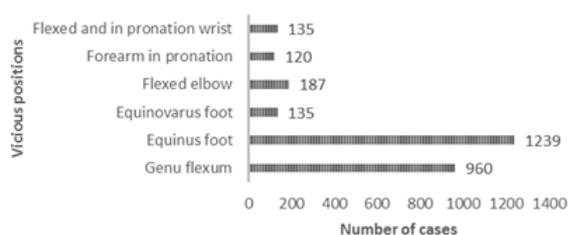


Figure 3.
Case repartition according to vicious positions

Vicious positions that were treated with botulinum toxin

Genu flexum. Genu flexum of over 10°. The possibility of surpassing the area of maximum spasticity. The hamstring and gastrocnemius muscles are injected.

Equinus foot. Equinus foot with a maximum dorsal flexion of -15°. Through passive movements exceeding the spasticity area and obtaining a dorsal flexion of at least 10°. Gastrocnemius and soleus muscles are injected.

Equinovarus foot. Fixed adduction of the foot comparing to the leg axis of 10 - 15° associated with the equinus modifications. Gastrocnemius, soleus and tibialis posterior muscles are injected (Figure 4) [13, 22].



Figure 4.
Equinovarus foot

Flexed elbow, flexed wrist, forearm in pronation.

The vicious positions of the upper limbs require a larger dose on every muscle group and the post injection recovery is less efficient than in the case of the lower limb. Biceps brachial, anconaeus epitrochlearis and if needed, the quadratus pronator muscle are injected (Figure 5) [23].



Figure 5.
Forearm in pronation, flexed wrist

Post injection, the affected limb segment is immobilized in a cast so that the toxin's effect would set in faster. Robert M Kay *et al.* stated in his studies that casting after injection accelerates the toxin's effect with longer lasting action [14]. Anaesthetic relaxation allows a total correction of the vicious position,

especially in the cases where toxin injection had absolute indications. The cast was kept for 7 days, according to the majority of literature data [5, 7]. Physical therapy procedures were started immediately after cast removal and re-evaluation was made at a 2 week interval.

Re-injection wasn't made sooner than 3 months. Adverse reactions were followed for each patient.

Their vast majority was in accordance to the data already published [21].

We have followed both general (fatigue, nausea, flu-like symptoms-fever, headache and cough) and local (rush, hematoma- probably a procedural adverse effect, prolonged muscle hypotonia, the lack of effect) adverse reactions (Table I) [12]. There were cases in which both local and general adverse effects were encountered.

Table I
General and local adverse effects

General			Local		
Nausea	Fatigue	Flu-like symptoms	Muscle hypotonia	Skin rush	Hematoma
57	364	84	259	42	21
3.04%	19.44%	4.84%	13.83%	2.24%	1.12%

In 73 cases (3.89%) there was an absence of botulinum toxin effect. From these, 60 were after reinjection and we attribute them to the appearance of antibodies. From the 13 cases without effect, in 3 we identified errors of applying the injection protocol (in 2 patients a longer period than the one stated by the manufacturer passed between the time the toxin was removed from the refrigerator and the moment of injection and in 1 case a lower dose than indicated by body weight was used) (Figure 6). It is possible that the rate of local adverse reactions to be higher, as cast immobilization could prevent their identification.

We evaluated the patients by clinical examination at 7, 14 and 30 days follow-up and we divided the results in three categories, as seen in Table II.

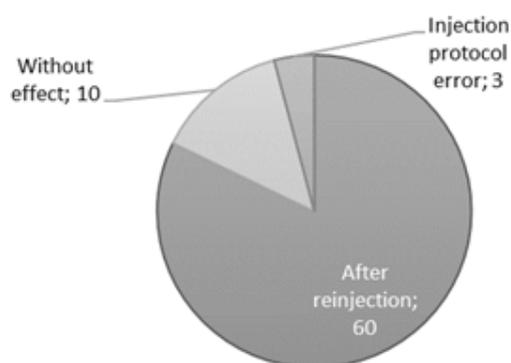


Figure 6.
Botulinum toxin effect absence

Table II
Results appreciation criteria

Excellent	Good	Failure
Effect onset in 14 days	Effect onset in 30 days	Absence of effect
Independent gait	Good motricity, sustained gait	Absence of post injection physical therapy results
Fine upper limb movements	Possibility of self-feeding	

The onset of toxin effect varied between 7 and 30 days (Figure 7). In 60 cases a lack of effect was observed after the second injection.

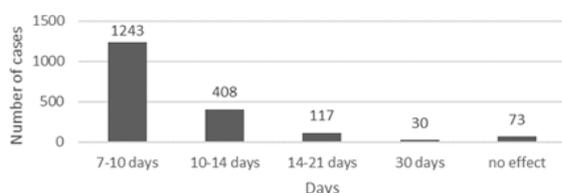


Figure 7.
The onset of toxin effect

did not influence the post injection evolution of the patients.

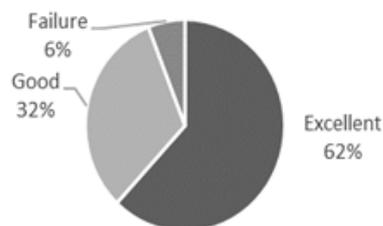


Figure 8.
Distribution of cases according to results

The distribution of cases according to results was: 62% excellent, 32% good, 6% failure (Figure 8). The general and local adverse reactions were encountered in 357 patients and spontaneously disappeared without any further treatment. Apart from the cases without any effect (0.72%), the adverse reactions

The results of our study tend to confirm the advantages of using Botulinum toxin A. In most cases we observed a decreasing in the muscle tone which allows optimal physical therapy and relatively normal development, avoiding the appearance of muscle retraction [26].

Muscle hypotonia, as an adverse reaction, was determined after cast removal and consisted of a decrease of muscle strength with 1 degree (measured on the scale of muscle strength). Disappearance of muscle hypotonia was spontaneous and concurrent with the start of physical therapy. In the cases of re-injection there was no case of muscle hypotonia. Some patients experienced nausea, adverse effect mentioned by the manufacturer but not found in most of the literature. Other patients experienced both nausea and vomiting but are difficult to link the appearance of these symptoms to either the product injected or the anaesthetic drugs.

Considering the outcome after Botulinum toxin administration, the results were divided into three appreciation criteria groups: Excellent, Good and Failure.

When dividing the results we took into consideration the time elapsed from the injection until the onset of the effect. We considered "excellent" the cases where the effect appeared within 14 days and the patient was able to sustain independent gait and gain fine upper limb movements. Even if the patients developed an independent gait after 14 days, we appreciated the results as being good. The study revealed that the patients, who benefited the most from the Botulinum toxin injection effects, were in the excellent group.

The injection effect is reversible putting us in the shelter of eventual diagnostic mistakes and in our study we have found no serious adverse reactions.

Conclusions

Botulinum toxin injection in the spastic muscle groups is an alternative to surgery and alcoholization of the nervous filets. Along with orthopaedic and recovery treatment, in most cases, the results are very good. In order to obtain the best effect, storage, transport and injection protocols must be respected. In most cases, re-injection will be necessary but only after 3 months.

The most important side effects that occurred were discrete muscle fatigue which disappeared within the first 24 hours after physical therapy was started and nausea that disappeared in 24 - 48 hours. The majority of side effects did not require additional treatment, local adverse reactions being less frequent than general.

There have been few cases in which botulinum toxin had no effect, most of them being at re-injection.

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