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Chapter 8

How Does Botulinum Toxin Injection and Physiotherapy Complement Each Other in Cerebral Palsy?

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Additional information is available at the end of the chapter

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Abstract

Cerebral Palsy (CP) is a clinical condition that describes impairments of motor and sensory systems due to a lesion in immature brain. CP-related disorders effect movements, balance and posture of the child. Spasticity is most frequent motor disorder seen in CP and effects 70–80% of the children with CP. Spasticity can lead to abnormalities in all motor system levels involving muscles, joints, bones and tendons. If spasticity exists for long period of time, immobilization of muscles in short position and changes in the connective tissue around joints lead to shortening of the muscles and connective tissue. Various methods are used for spasticity management in children with CP. Botulinum neurotoxin (BoNT) injections, oral medications, selective dorsal rhizotomy and intrathecal baclofen applications are the foremost among them. BoNT injections are most prevalently used one among these applications. BoNT, which is a neurotoxin obtained from *Clostridium botulinum* bacteria, is frequently used in children with CP to decrease muscle tone for a certain period in the selected muscles, prevent contractures, postpone surgery and decrease frequency of surgeries. During this time frame that muscle tone decreased, it is very important to increase activity and participation levels of children. For achieving better motor outcomes and functional independence, BoNT injections should be combined with physiotherapy (PT) and occupational therapy (OT).

Keywords: botulinum toxin, cerebral palsy, physiotherapy, spasticity, occupational therapy

1. Introduction

BoNT/A injections are one of the most frequently used methods to reduce muscle tone in individuals with CP. Given with clinical precision, BoNT/A has reversible chemo-denervation effects,

such that focal applications in selected muscles ensure selective muscle relaxation to intended muscles. BoNT/A was used in CP for the first time in 1993 by Koman et al. [1]. It has been used in gradually increasing rates since the day it was first used and in wider age ranges. The purpose of this section is to explain how BoNT injections and physiotherapy (PT) approaches complement each other. In this section, general information about CP, changes that occur in muscles due to spasticity, outcome measurements related with BoNT/A applications, combined usage of BoNT/A applications with PT and occupational therapy (OT) approaches, target muscles for injection, appropriate age range and side effects of injections will be discussed.

2. Cerebral palsy definition and classification

Cerebral palsy (CP) defines a group of permanent disorders of movement and posture development that causes activity limitation; these disorders are related with nonprogressive influence, lesion or anomalies that occur in developing brain. Disorders of communication and behavior, sensation, perceptional, cognitional problems and epilepsy generally accompany motor disorders of CP [2, 3]. These disorders affect body movements, balance and posture negatively [4–6].

Surveillance of Cerebral Palsy in Europe (SCPE) [2] classifies CP as spastic, dyskinetic and ataxic type based on the predominant neurologic findings. Majority (70–80%) of children with CP have spastic clinic characteristics. Increased muscle tone of the effected extremities, increased deep tendon reflexes, muscular weakness, tremor, abnormal posture and movement patterns, increased coactivation of antagonistic muscles, abnormal control of voluntary movement and associated movements and stereotypical movements are seen in spastic type [7–9].

Classification of children with CP according to anatomic pattern and special neuromotor effect is crucial for the treatment of motor disorders [10]. The most important major classification in children with CP is the classification made according to the anatomic pattern of effect. Hemiparesis, where only half of the body is affected; diparesis, where lower extremities are affected basically and upper extremities are affected slightly; and quadriparesis, where all extremities are affected, are the most widespread definitions [10]. In recent years, the idea suggested by SCPE for the spastic type has started to be accepted for CP classification; as "unilateral spastic CP" where a single side of the body is affected or "bilateral spastic CP" where both sides are affected [2].

3. Spasticity

Spasticity, widely seen in CP, is the increase of physiologic muscle tone. Spasticity can occur in different forms depending on the formation time, location, size and diffuseness of the lesion in the developing central nervous system [11].

Fibrous contractures inside muscle or connective tissue around joints originating from spastic extremity posture, which are forming over time, compromise the increased response of the muscle against passive stretch and are one of the reasons of increased muscle tone. Muscle

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contractures and spasticity generally complicate patient care and reduce extremity functions and motor capacity [11–13].

CP is caused by nonprogressive lesion in the brain but accompanying spasticity, reduced muscle strength, muscle length changes, abnormalities in joint movements, functional capacity deficiencies and many situations like this are not static and can change over time with growth. Musculoskeletal system pathologies may start to cause greater problems as child grows. For normal muscle growth, elongation of the muscle under physiological overload is necessary. A hypertonic muscle, unable to relax, will eventually fail to grow and develop with the normal elongation of the bone in a child. Increase in height and weight of the child can contribute to musculoskeletal system problems. Spasticity can cause contractures and torsional deformities due to the growth in bones and muscles not being in proportion. Moreover, instability and early osteoarthritic changes can be observed in joints. As the individuals with CP grow, abnormal biomechanical situations affecting joints and static postures can cause pain formation. As the child grows old, chronic pain, social isolation, functional limitations and dependency can affect mental status negatively [7, 14].

4. Tone inhibition in children with CP

BoNT/A injections relax muscles by blocking acetylcholine release, with pharmacologic effect occurring in 48–72 h, but which wanes 3–4 months later [7]. However, this period when tone decreases gives an opportunity for therapeutic approaches [7, 15]. BoNT/A injections in children with CP are generally combined with PT and OT, while trying to achieve better rehabilitation outcomes. This complementary application has been accepted generally because it can be applied to the spastic muscles directly and the amount of the toxin can be adjusted per muscle, and it has rapid effect and has only a few side effects [16, 17]. But tone reduction alone is not enough for gaining functional outcomes. Applications such as stretching and strengthening the muscles, weight bearing on extremities and practicing daily life activities are essential. Children need to continue an intensive physiotherapy program before and after the BoNT/A application for achieving functional improvements [18].

Many studies investigate to maximize this effect of BoNT/A injections. In this perspective, combined usage of PT and BoNT/A has been discussed. This temporary effect of BoNT/A can be increased by activity-based physiotherapy and rehabilitation programs [15]. The decrease of tone by selective chemodenervation of overactive muscles presents an opportunity to extend muscle length, prevent contracture formation, strengthen antagonistic muscles, introduce new movement strategies to children and improve motor and functional skills [19, 20].

It was reported that PT and OT approaches that are used in children with CP in combination with BoNT/A injections are conventional PT, conventional OT, constrained induced movement therapy (CIMT), hand-arm bimanual intensive training (HABIT), casting, active/passive stretching exercises, strengthening exercises, neurodevelopmental approach (Bobath), robotic rehabilitation and mobility and walking training [15, 21–25].

Although the benefits of BoNT/A injections with PT and OT combinations are mentioned in many studies, optimal intensity and dosage of the therapies to be applied is not known [16]. According to expert opinion and consensus reports, PT following BoNT/A injections must consist of functional motor training, serial casting, stretching and strengthening exercises [26–28]. According to the literature, PT and OT programs can be followed-up as individualized therapy, group therapy, distance learning or a home program by family education [29–31].

5. Classification in CP

Classification systems have been developed to determine the severity of functional limitations in CP. The most important and widely used one of these systems is the Gross Motor Function Classification System (GMFCS) developed by Palisano et al. (1997). This system comprises five levels: level I expresses the best level of gross motor function and level V expresses the most influence in motor function. According to this system, the children in level I can walk independently, and the children in level V cannot sit independently without a support and cannot protect their head and body postures against gravity [32].

It is reported that BoNT/A application is used generally in ambulant hemiplegic and diplegic children with mild or moderate motor influence. The reason for an increase usage in this population depends on the acquisition of greater functional gains of these children [33]. In mildly affected children, tone of the spastic, active and nonfibrotic muscles can be decreased until 12–16 weeks [27, 34, 35]. In children with severe motor disorders, on the other hand, this gain is more limited. In children who are at GMFCS level 4–5, even very simple tasks used in daily life could generate problems and affect quality of life negatively [36, 37]. Although BoNT/A injections are used in these children to facilitate active movement, to ease their care and to decrease pain, there are not adequate evidences reporting the effect of these applications [33].

Researchers report that small children with CP at GMFCS level I–II show better development in gross motor function, on the other hand, older children in GMFCS level III–IV show less development in gross motor function or no development at all. The possibility of development of contractures in older children with worse gross motor function level diminishes benefiting possibility from BoNT/A injection. Especially in GMFCS level IV–V children, dysphagia, respiration problems, brain stem pathology and cranial nerve influence accompany more and therefore it is reported that BoNT/A dose for these children must be adjusted very carefully [27, 34].

6. Physiotherapy and occupational therapy approaches frequently used in CP

The purpose of therapy in CP is to improve functionality, support skill development and locomotion, sustain health in terms of social interaction and independency and to prevent possible deformities. Best results are achieved by early intense intervention. For an effective treatment program, team approach including physiotherapy, occupational therapy, behavioral therapy, pharmacological and surgical treatment, adaptive equipment and therapy and

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treatment of related health problems is necessary. The purpose of all treatment methods is to improve independency of the child [7, 10].

PT and OT applications start at birth and continue through life span to minimize sensory and motor disorders, to support normal motor development of the children, to improve activity and participation, to facilitate activities of daily life and to reduce load of family and caretakers. However, increased muscle tone, whose negative effects were mentioned in detail above, complicates physiotherapy and OT applications and is shown as one of the reasons of unresponsiveness to PT in children with CP [19]. Therefore, PT and OT approaches must be combined with applications helping tone control such as BoNT/A injections. Most frequently used physiotherapy approaches in children with CP are neurodevelopmental treatment (Bobath); based on normal sense-motor development of children, Vojta; using reflex stimulus points, Avres; suggesting that sensory-motor integration and organization is the basic of psychomotor development and conductive education (Peto), where intensive training programs are applied in the management by a leader and Goal Directed Therapy determining individual targets [18]. Numerous different therapy methods including electrotherapy applications, muscle strengthening and stretching exercises, orthotics, adaptive equipment and serial casting can also be used along with these approaches.

7. Evidences on physiotherapy approaches in combination with BoNT/A injections

BoNT/A injection in CP is considered as a selective tool to reduce spasticity. Appropriate selection of the patient, treatment dosage and muscles is crucial for effective injections [19]. In the scope of the International Classification and Functioning (ICF), BoNT/A injections affect body structures and functions; however, when it is combined with physiotherapy, it causes changes in the activity level as well [16]. The effectiveness of physiotherapy programs changes based on the application period and intensity [15]. Moreover, experience and knowledge level of physiotherapist, context of home program and conformity of the families to home program is crucial for the effectiveness of the treatment. There is no consensus on the type of exercises, or rehabilitation methods should be used to maximize the effects of tone reduction following BoNT/A applications. It is reported that orthotic management, serial casting and intensive physiotherapy are the most significant factors to benefit the most from the injection effect [19, 38].

It is reported that age of the patient, therapy applications and casting are crucial factors improving success following BoNT/A injections [39]. Inclusion of especially strengthening exercises and targeted motor training within the physiotherapy program is suggested [27].

The effects of PT + BoNT/A injections are reported as the reduction in spasticity, increase in dynamic and passive range of motion, improvement in selective motor control, improvement in strength, improvement in function and task performance and reduction in pain [27].

There are numerous studies in the literature investigating the usage of PT and BoNT/A applications together. In a study, the effectiveness of BoNT/A injections in long term with and without physiotherapy was determined. One of the groups received regular PT (two times a week) while other group received intensive PT. It was reported that gross motor function showed more improvement in the intensive PT group at the end of 1 year. Although tone increased after a period, gross motor function scores were preserved. It has been emphasized that BoNT/A injections decreased muscle tone in children with CP and when combined with PT the benefits of this application improved (Jianjun, Shurong et al. 2013).

In a study comparing the influence the two different PT methods, an intense physiotherapy program consisting of NDT (focusing on motor development and function) was applied to a group while conventional intense physiotherapy program (focusing on muscle length and strength) was applied in the other group. It was reported that the children benefited from both interventions; however, the success in NDT group was higher in terms of reaching the determined targets [19].

Chaturvedi et al. compared two groups of children with CP; one group received PT and other group received PT + BoNT/A injection. After 6 months of rehabilitation, they reported that gross motor function improved in both groups and also there was increase in the sensory and motor fiber diameter measured by diffusion tensor tractography; in other words, brain plasticity improved. They discussed that BoNT/A injections made as an addition to PT did not affect the result in 6 months [15].

Improvement of hip abduction angle, popliteal angle and passive dorsal flexion was reported in individuals who received intense physiotherapy including use of ankle foot orthosis (AFO) after BoNT/A application [40]. In a research conducted on 29 children with CP and spastic equinus deformity, it was reported that tone reduction and dorsal flexion improvement was good in cases which were applied BoNT + PT and serial casting and their effects were preserved in the long terms in comparison to the cases which were applied only BoNT + PT. However, in this study, PT program only includes stretching for ankle. Lack of an extensive physiotherapy program may have affected the results. In this study, the authors reported the pressure ulcers in three patients as negative effects of casting and failure to do exercise when casting was made was reported to be a disadvantage. They suggested to apply weight-bearing and isometric exercises during the casting period [41].

In a study measuring muscle activation patterns with surface electromyography (sEMG) after BoNT/A application combined with intensive PT, it was reported that this combination had positive effects on walking kinematics but had no effect on muscle activation patterns [42].

In 47 children with spastic CP who were applied PT (stretching of flexor muscles, strengthening extensor muscles, functional mobility training) for 12 weeks following multilevel BoNT/A injections for lower extremity muscles, it was reported that gross motor function measured by Gross Motor Function Measurement (GMFM) improved, and this improvement was preserved up to 1 year; however, there was no change in energy consumption [38].

PT applied in 71 children with CP consists of stretching of flexor muscles, balance training and walking training (five times a week in the first 3 weeks and three times a week during

the following 8 weeks); along with multilevel BoNT/A injections at the lower extremities, it was reported that the muscle tone decreased in the follow-up in the first 3 months; however, this was not preserved in the follow-up in the 6 months and the improvement in gross motor function that was measured by GMFM was sustained in both 3 and 6 months [43].

According to a review conducted in 2009, it was reported that BoNT/A is an effective application for decreasing spasticity and functional improvements can be achieved with time limitation. However, the follow-up periods were up to 6–24 weeks in many studies and this made it difficult to determine long-term effects and the effects of the repeating injections [44]. In contradicting with the former review we mentioned, in a systematic review conducted in 2011, BoNT/A injections made separately or in combination with casting were not suggested; it has been discussed that there is not adequate evidence on the combinations of BoNT/A injections with PT and usual care [45].

In researches where BoNT/A injections are applied along with PT, failure to explain adequately the content and period of the applied physiotherapy approaches, which modalities were used and who performed the PT applications makes it difficult to select the most correct therapy approach to be combined with BoNT/A injections. Methodological differences can explain the different results obtained in these studies. However, as proven in the above given studies, it is observed that the integration of the two applications resulted with especially improvement in gross motor function in children with spastic CP.

8. Evidences on occupational therapy approaches in combination with BoNT/A injections

The greatest problem faced when working with children with unilateral spastic CP is the rehabilitation of paretic upper extremities. These children manage to stand up and walk more easily and spontaneously in general. Numerous different reasons such as spasticity, shortness and weakness of upper extremity muscles, limited joint movement, rotational deformities in the forearm and wrist bones, decreased unilateral skills, inadequate motor control and sensory problems affect functional development of the affected extremity in children with unilateral CP [46].

CIMT aiming to facilitate intense usage of the affected extremity and limiting the healthy extremity usage; HABIT facilitating combined usage of both extremities, and Goal Directed Therapy, determining individual targets have been reported during the recent years as evidence-based applications improving upper extremity activities following BoNT/A injections [47–49].

The purpose of the post injection therapy is to ensure motivation and new experiences and form an environment where the children can use their affected arm [50]. There are studies reporting that usage of the affected upper extremity in children with unilateral CP does not improve when BoNT /A injections are made separately without combining with the therapy [51].

In a study comparing the two groups who were applied modified CIMT and OT approach supporting bimanual activity following BoNT/A injections in children with unilateral CP,

improvement was achieved in upper extremity performance, functional skills, occupational performance and goal attainment, and the groups were not superior to one another. Therefore, it is suggested that clinicians divert to specific goals and select the family friendly and comfortable application [52].

In a randomized controlled study, a group which was applied OT following BoNT/A injection and another group which was only applied OT was compared, and it was reported that more successful result in terms of bimanual performance was obtained in the group which was applied OT in combination with BoNT/A. The authors reported that there was improvement in terms of activated range of motion and goal performance in both the groups. However, they reported that in the ICF framework, the improvement in each domain was observed only in the group applied OT after BoNT/A injection [53].

According to a Cochrane systematic review published in 2010, it was emphasized that BoNT/A injection combined with OT in children with CP and having unilateral influence was more effective in reducing the disorder and improving activity level in comparison to only OT [51].

9. Appropriate muscle selection in CP

Existing pathologies of the children are considered for the selection of the muscles to be injected, and generally BoNT/A injection need to be made for more than one muscle at the same time in general to obtain change in walking and other functional activities [34, 54]. BoNT/A injections are applied most frequently for equinus and equinovarus deformities, knee and hip flexion spasticity, adductor spasticity and spasticity of the upper extremity (e.g. finger flexion, wrist flexion, ulnar deviation, elbow flexion and shoulder adduction injection). In ambulant children with CP, generally walking pathologies are considered for the selection of the muscles to be injected. In children those who have spastic equinus, injections are made mostly to gastrocnemius and soleus muscles; in those who have jump gait to gastrocnemius, soleus and hamstring muscles; in those who have scissoring and jump gait to gastrocnemius, soleus, hamstrings and adductor muscles; in those who have scissoring to hamstrings and adductor muscles; in those who have spastic knee flexion to hamstrings and in those who have only scissoring to adductor muscles [15, 22, 35, 55].

The reason for more frequent usage of BoNT/A injections in lower extremities is explained as containing fewer fine skills, improving movement and gaining better functionality to the children during their daily life activities [33]. Complexity of neural motor control during upper extremity functions limits the usage of BoNT/A injections in upper extremities [56].

10. Evaluation in CP

Various assessment methods are used in CP to evaluate combined effects of PT, OT and BoNT/A applications. Tone assessments are the major ones among these. There are various clinic scales, biomechanical evaluation tools and neurophysiologic evaluation methods to

ICF domain	Assessment tool
Body structures and function	Active and Passive ROM Ashworth/Modified Ashworth Scale Dynamic Sonoelastography Electromyography Goal Attainment Scale (GAS) Gross Motor Function Measurement (GMFM) Manuel Muscle Testing The Quality of Upper Extremity Skills Test (QUEST) Physician's Rating Scale (PRS) Selective Motor Control Assessment Tardieu/Modified Tardieu Scale Three-Dimensional Gait Analyses Visual Analogue Scale (VAS) WeeFIM_ (Functional Independence Measure)
Activity/participation	Gross Motor Function Measurement (GMFM) *Assisting Hand* Assessment (AHA) ABILHAND-Kids Questionnaire Bimanual Fine Motor Function (BFMF) Child Health Questionnaire (CHQ) Edinburgh Visual Gait Score (EVGS) Energy Expenditure Measures Goal Attainment Scale (GAS) Manual Ability Classification System (MACS) Observational Gait Scale Physician's Rating Scale (PRS) Six-Minute Walk Test The Quality of Upper Extremity Skills Test (QUEST) The *Canadian Occupational Performance Measure* (COPM) Three-Dimensional Gait Analyses Visual Analogue Scale (VAS) WeeFIM_ (Functional Independence Measure)
External/personal factors	*Goal Attainment Scaling* (GAS)

Table 1. Outcome measurements used in children with CP to assess effects of BoNT/A injections.

evaluate spasticity; however, there is no consensus about how spasticity can be evaluated the best. The most frequently used clinical scales are Ashworth/Modified Ashworth and Tardieu/Modified Tardieu scales [57, 58]. However, reliability of these scales is questioned. In a study, it was reported that for assessing medial hamstrings spasticity, MTS and MAS were less sensitive in comparison to the sEMG in the determination of changes following BoNT/A injection [59].

In addition, there are scales such as Spasticity Grading, Modified Composite Spasticity Index, Duncan Ely Test, New York University Tone Scale and the Hypertonia Assessment Tool (HAT) [60–62]. As biomechanical evaluation tools, myotonometer, sensors, Wartenberg Pendulum Test, dynamometer, goniometric measurement and robot supported evaluation tools are used [61, 63–67]. Electromyography, tonic stretch test and soleus muscle Hoffmann reflex (H-reflex) are neurophysiologic evaluation methods that could be used in spasticity evaluation [61, 68, 69].

In addition to spasticity, changes in muscle length, normal motor development and functions are also evaluated. According to the literature, the most frequently used measurement tools in this respect are Gross Motor Function Measure evaluating gross motor function, Three-Dimensional Gait Analyses, Six-Minute Walk Test and Physician's Rating Scale (PRS) evaluating walking parameters, electromyography evaluating muscle activations, dynamic sonoelastography evaluating intrinsic characteristics of muscles, *Assisting Hand* Assessment (AHA), The *Canadian Occupational Performance Measure* and The Quality of Upper Extremity Skills Test evaluating upper extremity functions, *Goal Attainment Scaling* evaluating the level of reaching the determined targets and The Pediatric Evaluation of Disability Inventory measuring functional independency. Also active and passive range of motion, selective motor control and manual muscle strength measurement are in use for this population. The distribution of the measurement tools that are used most frequently in publications based on ICF dimensions is shown in **Table 1** [17, 19, 24, 25, 34, 38, 49, 52, 53, 55, 70–75].

11. Changes occurring in the intrinsic structure of muscle with BoNT/A injection

It was reported that increased stretch reflex response of spasticity had both neural and nonneural components. Motor unit and reflex activity formed against muscle length growth is indicated as the neural foundation, and mental status, stress, fatigue, decreased sarcomere number and decreased flexibility, muscle stiffness and high collagen content in spastic muscle are indicated as the nonneural components [76, 77].

Positive effects targeted with BoNT/A injections on neural characteristics of muscles and therapy targeted on passive and active characteristics; therefore, combinations of these applications are suggested [33].

In a child with spastic diparetic CP, it was reported that muscle stiffness diminished, gross motor function improved and tone measured with MAS decreased after BoNT/A injection to gastrocnemius muscle combined with physiotherapy including electro stimulation, stretching and strengthening exercises applied twice a day for 4 weeks [70]. In another study conducted on children with spastic diparetic CP with the same design, it was reported that intrinsic stiffness of muscles decreased at the end of 4 weeks [77]. Some authors discussed that spastic muscle relaxation facilitates extremity growth and decreases fixed contracture development [57, 77, 78].

In animal experiments, it was shown that muscle and tendon growth and function was close to normal following BoNT/A injection; however, it caused reduction in bone mineral density [79]. It was reported that in some animals, BoNT/A injections made to nonspastic muscles prevented normal growth of muscle and caused progressive and persistent atrophy of muscle. In another study, it was reported that atrophy caused by BoNT/A injection was not reversed by exercise training [80, 81]. There are studies reporting that injections can cause decrease in muscle strength in children with CP; nevertheless, it was reported that there was 4–5% decrease in muscle volume by injections made to gastrocnemius muscle in 15 children with CP, and this was not as dramatic as in animal experiments [73, 82]. It was reported that

BoNT/A injections change muscle tone in the active, nonfibrotic and noncontractured sections of muscle and allowed stretching of muscle by decreasing tone, and this in turn was a stimulus for muscle growth. It was indicated that BoNT/A injection decreases agonist activity, supports antagonistic activity and must be combined with therapy to improve function, activity, participation and motor development in children with CP [34].

12. Age range

Spasticity develops in the first few years in children with CP. BoNT/A injections are suggested during 2–6 years of age while walking patterns and motor functions are prone to development [28]. According to a study conducted on 189 children with spastic CP in 2011, it was reported that the increase in dorsiflexion angle following BoNT/A injections made to triceps sure depended on the injected dosage and patient's age. It was reported that the obtained effect was as good as the children was younger [83]. There are limited reports about the usage of BoNT/A injections before 2 years of age. Usage in cases of 1 year 10 months of age was reported as the earliest [35]. BoNT/A was applied in children with CP younger than 2 years of age in very few studies, and in these studies, the effectiveness of the application was not analyzed separately for these children. Information is needed about the potential benefits or reliability in this age group [79].

13. Side effects

There are numerous studies scrutinizing the therapeutic benefits of BoNT/A injections in children with CP; however, there are limited publications about their safety. There were side effects observed depending on the application in 1–2% of children who were applied BoNT/A injections. Some authors consider neutralizing antibodies as responsible for side effects that develop after toxin injection. Formation of these substances increases BoNT/A amount that needs to be applied in the next injection. However, a single injection is not sufficient for many children and the injections need to be repeated in intervals of approximately 6 month intervals. In a research, it was reported that 58% of 4000 injections made during 15 years were first injections, 42% were second and the following [35].

In various researches, side effects of BoNT/A injections were reported as flu-like symptoms, nausea, diplopia, dysphagia, aspiration, respiratory tract infection, bronchitis, pharyngitis, pneumonia, asthma, generalized weakness, muscle weakness, urinary incontinence, falls, seizures, fever and unspecified pain [27, 84]. The start of systemic reactions can vary between the moment right after injection to a few weeks. There are studies reporting that urinary incontinence disappeared within 1–6 weeks. A relationship was found between BoNT/A dosage and hospitalization due to respiratory or urinary problems. It was reported that urinary and pulmonary problems that developed could be caused by systemic spread [35].

General anesthesia can increase side effects because anesthesia is a major risk factor for aspiration and infection. It could be difficult to distinguish whether the side effects occurred from BoNT/A or general anesthesia in the applications made under general anesthesia [35, 85].

It was reported that severity of the side effects related with the toxin was low; however, the number of side effects in children with CP were higher in comparison to other users. There are only a few studies reporting mortality following BoNT/A injections [86]. In literature, there are many studies about the positive effects of injection; however, there is inadequate information about optimal dosage, injection schemes and safety concerns [54].

Although injections generally have a good safety profile in short term, it is not suggested to use high doses in patients who have epilepsy or immune problems. It was reported that the children who were at level IV–V in GMFCS and had laryngeal and pharyngeal dysfunction were under more risk in terms of side effects [35, 85]. Further studies are needed to determine the relationship between especially mortality and epilepsy and BoNT/A injections [84].

The start of systemic reactions can vary between the moment right after injection to a few weeks. General anesthesia can increase side effects because anesthesia is the major risk factor for aspiration and infection. It could be difficult to distinguish whether the side effect stem from BoNT/A or general anesthesia in the applications made under general anesthesia [85].

In this section, it is understood that BoNT/A is a safe tool to decrease muscle tone in children with spastic CP and are effective in improving gross motor functions of children when combined with PT, OT, serial casting and orthesis. The injections have relatively few side effects, caring about patient selection and the dose to be applied should minimize side effects of the application. Further studies are needed to clarify what type of changes the injections cause in the architecture of spastic muscle in children with CP. Children with CP must be treated in a multidisciplinary setting where many specialists work together by combining many treatment approaches.

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