The Effect of Botulinum Toxin- A injection for the Lower Limb in Children with Spastic Cerebral Palsy

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Objectives: To investigate the effect of botulinum toxin-A (BoNT-A) on the age groups and gross motor function classification level in children with cerebral palsy (CP).

Method: In this study, 116 children with spastic CP were investigated. BoNT-A was injected into the spastic muscles of the lower limbs of all participants. All participants received physiotherapy and functional electrical stimulation for 3 months after injection. We measured the change in spasticity using the Modified Ashworth Scale and gross motor function using the GMFM-88. Spasticity was measured before injection and at 1 and 3 months after injection. Measurement of gross motor function was performed before and after the injections.

Results: The effect of BoNT-A injection in combination with physiotherapy and electrical stimulation significantly improved spasticity and gross motor function. After BoNT-A injection, younger children showed reduced spasticity and improved gross motor skills compared to older children. At the gross motor level, sitting, standing, and walking improved in children with gross motor function classification levels I-III, and posture and mobility improved in children with gross motor function classification levels IV-V.

Conclusions: We conclude that BoNT-A injection is effective for improving gross motor function in patients younger than 72 months of age.

Keywords: Neurotoxin, Spasticity, gross motor function, Physiotherapy, Electrical stimulation

Introduction

Cerebral palsy (CP) refers to a group of permanent disorders of movement and postural development that result in activity limitations due to non-progressive injuries to the developing fetal and infant brain [1]. Of these children with CP, approximately 70% to 80% have spasticity, resulting in abnormal motor function and limited activity and participation [2]. Spastic CP is the most...
common cause of motor disability in childhood [3]. The disability of a child is classified by the Gross Motor Function Classification System (GMFCS) [4]. The GMFCS is valuable and reliable for classifying CP children into age-related gross motor functions [5]. Specifically, the Gross Motor Function Measure (GMFM-88) [6] is a clinical observational tool that measures changes in gross motor function [7]. A comprehensive assessment of spasticity was provided using the Modified Ashworth Scale (MAS) [8].

Management of spasticity in CP involves multidisciplinary interventions to increase functionality, maintain health, and improve quality of life. These include physical therapy, occupational therapy, orthotics, surgical interventions, and pharmacologic agents such as botulinum toxins [9]. Besides, the international consensus [10, 11] recommends the appropriate use of BoNT-A injections, including treatment algorithm doses, injection techniques, target muscles, and their safety and efficacy in the pediatric population.

Botulinum toxin-A (BoNT-A) is a solid option in the interdisciplinary treatment of spasticity, providing focal reduction of muscle tone in CP patients [9]. By inhibiting the release of acetylcholine at synapses, BoNT-A reduces muscle stiffness, increases joint range of motion, relieves pain, and improves function [12]. BoNT-A can be injected into the spastic muscle by palpation, electromyography (EMG), electrostimulation (ES), or under ultrasound (US) guidance [13]. Under US and EMG guidance, the injections are 90-99% effective even in small muscles [14]. However, because the injection in EMG-guided infusion is painful, it is usually performed under general anesthesia for adults and children. The US guidance seems to be a good alternative for use in children with CP: it allows identification of the muscle to be injected and verification of the position of the needle tip in the muscle [15, 16].

Comprehensive rehabilitation management is required to optimize the reduction in stretch-induced by BoNT-A injection. In particular, active and passive stretching of the target muscle and strengthening of the antagonist muscle are needed after the injection [17]. Additionally, physiotherapy (PT) and functional electrical stimulation (FES) are indicated to improve muscle strength and length. The denominator of comprehensive rehabilitation can summarize all these treatment options (casting, orthoses, PT, FES) [17-19].

In several studies, treating with BoNTA before comprehensive rehabilitation did not add to the clinical effectiveness of rehabilitation. Thus, BoNT-A prescription and use should be critically reconsidered by age group and GMFCS subgroup in cerebral palsy [17,18,20]. In Mongolia, there is a lack of research on the outcomes of rehabilitation of children with cerebral palsy; there is only one study on the outcomes of spasticity management and Botulinum toxin-A injection in children with CP [21]. Therefore, the purpose of our study was to investigate the efficacy of spasticity management on the GMFCS level and the age group in children with cerebral palsy (CP).

Materials and Methods

Study design
This study is based on a quasi-experimental research conducted from November 2018 to January 2022 at the outpatient rehabilitation clinic of Mongolia-Japan Hospital, Mongolian National University of Medical Sciences. We followed and collected data over time for three groups of participants who received adjunctive therapies after BoNT-A injections. We evaluated the outcome of adjunctive therapies before BoNT-A injection and during adjunctive therapies at 1 and 3 months and compared the three groups. A quasi-experimental study is an intervention study and differs from a clinical trial in that it differs in randomization and blinding. The interventional design can evaluate our study aims concerning both therapeutic agents (e.g., treatments) and prevention (e.g., management) and is also more likely to be free from biases [22, 23].

Participants
315 children with CP who had attended the outpatient rehabilitation clinic were registered and examined. Children with spastic CP who met the following inclusion criteria based on medical records and clinical examination: 1) age 24-216 months, 2) diagnosis of spastic hemiplegic, diplegic, and quadriplegic CP, 3) no fixed contractures, and 4) ability to understand and follow commands. The exclusion criteria were: 1) chemodenervation treatments within six months, 2) previous selective posterior rhizotomy or orthopaedic surgery, and 3) diagnosed epilepsy. In addition, children allergic to the toxin were excluded. Finally, 116 children with CP (14 hemiplegic, 79 diplegic, 23 quadriplegics; 47 girls, 69 boys) whose GMFCS level was I-V (GMFCS level I/II/III/IV/V: 4/38/57/9/8) met the inclusion criteria and were invited to participate in our study (here Table 1).
Table 1. Characteristics of the study participants

<table>
<thead>
<tr>
<th>Demographics, baseline clinical characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (months)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;72</td>
<td>64(55.2)</td>
</tr>
<tr>
<td>72-144</td>
<td>38(32.8)</td>
</tr>
<tr>
<td>144&lt;</td>
<td>14(12.1)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69(59.5)</td>
</tr>
<tr>
<td>Female</td>
<td>47(40.5)</td>
</tr>
<tr>
<td><strong>CP types</strong></td>
<td></td>
</tr>
<tr>
<td>Quadriplegia</td>
<td>23(19.8)</td>
</tr>
<tr>
<td>Diplegia</td>
<td>79(68.1)</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>14(12.1)</td>
</tr>
<tr>
<td><strong>GMFCS</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4(3.4)</td>
</tr>
<tr>
<td>II</td>
<td>38(32.8)</td>
</tr>
<tr>
<td>III</td>
<td>57(49.1)</td>
</tr>
<tr>
<td>IV</td>
<td>9(7.8)</td>
</tr>
<tr>
<td>V</td>
<td>8(6.9)</td>
</tr>
<tr>
<td><strong>Age, mean±SD</strong></td>
<td></td>
</tr>
<tr>
<td>82.8±43.1</td>
<td></td>
</tr>
<tr>
<td><strong>Child weight, mean±SD</strong></td>
<td></td>
</tr>
<tr>
<td>21.3±10.6</td>
<td></td>
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</tbody>
</table>

CP - cerebral palsy; GMFCS - gross motor function classification system

**Intervention**

According to the recent international consensus on using BoNT-A injections [10], all 116 participants had one round of ultrasound-guided injections of BoNT-A (Neuronox®, Medytox Inc., Korea) to the targeted spasticity muscle. The total dose ranged between 50 and 380 units (U) of BoNT-A (0.8 to 3.6 U/kg), using 4 ml of normal saline to deliver a solution containing 50 U/ml. BoNT-A was injected at the medial and lateral heads of the gastrocnemius (GCM), the medial hamstrings (MH), and the hip adductors (HA). In each muscle, two site injections were performed (1.5 to 3.6 U/kg).

Furthermore, other injected muscles, including the tibialis posterior, were injected at one site (0.8 to 1.5 U/kg). All participants received physiotherapy and functional electrical stimulation under ultrasound for three months after the BoNT-A injection. Physiotherapy included various muscle strengthening and stretching exercises for 20-30 minutes, 3-5 times per week. FES was applied to the injected muscles to reinforce the BoNT-A injections one week after injection. FES was applied to the antagonistic muscles from the second week to enhance their strengthening. FES lasted 30 minutes for each participant.

**Outcome measures**

We measured the changes in (1) spasticity and (2) gross motor function in each participant. Pre- and post-injection measurements are essential for study participants to review changes in spasticity and gross motor function [24, 25].

(1) **Measurement of changes in spasticity**

Lower limb spasticity was measured using the MAS [8]. The measured muscles were bilateral or unilateral hip adductor, knee flexor, and plantar flexor. Spasticity was measured using the MAS[8], a 6-point rating scale with a range of 0 to 4. To analyze statistically, a MAS grade of 1+ was altered to the MAS grades 2, 3, and 4 were also altered to 3, 4, and 5. Spasticity was assessed pre-injections and then 1- and 3-months post-injections.

(2) **Measurement of changes in gross motor function**

We measured changes in gross motor function of the participants using the GMFM-88 [6]. The 88 items of the GMFM-88 are grouped into the following five dimensions: (A) lying and rolling, (B) sitting, (C) crawling and kneeling, (D) standing, and (E) walking, running, and jumping. Besides, the items are scored on 4-point ordinal scales (0=does not initiate, 1=initiates, 2=partially completes, and 3= completes). Each participant was
screened to allow a maximum of three trials for each item [6]. Furthermore, changes in gross motor function of the participants were assessed through observation by giving verbal instructions in the physiotherapy room and using some necessary equipment (e.g., mats, stairs and balls). We organized this measurement during pre-injections and then 3 months post-injections.

Statistical analysis

We recorded the following information on our study form and then exported it into Excel: age; gender; weight; CP type; GMFCS level; target muscle group; dose of BoNT-A injections; pre-injection and 1- and 3-months post-injection assessment using the MAS [26]; and pre- and post-injection assessment using the GMFM-88 [6]. Two independent researchers checked all exported data for bias. Afterward, the data was analyzed using STATA 16 software.

Descriptive statistics were presented as mean and standard deviation (SD) for continuous variables. Categorical variables were expressed as numbers and percentages. The Kolmogorov-Smirnov test calculated the distribution of continuous variables. Furthermore, we used Student’s t-test to describe the change in the score of continuous variables between the groups. Repeated analysis of variance (repeated measures ANOVA) was used to assess changes over three months for each group. In addition, a mixed effect model in repeated measures ANOVA was used to evaluate whether the therapy method affected the results of 3 months post-injection. The least significant difference (LSD) test is a multiple-comparison correction used when several dependent or independent statistical tests are performed simultaneously. The least significant difference (LSD) test is used in the context of the analysis of variance when the F-ratio suggests rejection of the null hypothesis H 0, that is, when the difference between the population means is significant. If the p-value of the hypothesis test was less than 0.05, the alternative hypothesis is considered statistically significant.

Ethical statement

This study received ethics approval from the Mongolian National University of Medical Sciences in Ulaanbaatar, Mongolia (2018/3-16). Each participant’s parent confirmed their interest and signed an informed consent form before our prospective interventional study.

Results

Changes in gross motor function

Table 2 summarizes changes in the gross motor function of the participants in the ambulant (GMFCS I-III) and non-ambulant (GMFCS IV-V) groups. Three months post-injection, the gross motor function of the participants in each group showed statistically significant improvement. Among them, the ability to lie and roll (A) improved in the non-ambulatory group, while the ability to sit (C), stand (D), walk, run, and jump (E) improved more in the ambulatory group. However, concerning the abilities to crawl and kneel (B), both groups improved equally, with no statistical difference (p=0.084).

<table>
<thead>
<tr>
<th>GMFCS-88 dimensions</th>
<th>Ambulant (GMFCS I-III), change of score</th>
<th>Non-ambulant (GMFCS IV-V), change of score</th>
<th>P value&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10.8±6.6</td>
<td>7.35±3.60</td>
<td>0.003</td>
</tr>
<tr>
<td>Lying and rolling (A)</td>
<td>0.06±0.42</td>
<td>2.71±0.44</td>
<td>0.0001</td>
</tr>
<tr>
<td>Crawling and kneeling (B)</td>
<td>1.22±3.21</td>
<td>2.65±0.47</td>
<td>0.084</td>
</tr>
<tr>
<td>Sitting (C)</td>
<td>2.22±0.76</td>
<td>0.88±0.65</td>
<td>0.022</td>
</tr>
<tr>
<td>Standing (D)</td>
<td>3.36±0.31</td>
<td>0.71±0.26</td>
<td>0.0001</td>
</tr>
<tr>
<td>Walking, running, jumping (E)</td>
<td>3.93±0.34</td>
<td>0.41±0.07</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

GMFCS- gross motor function classification system, †-Student’s t-test
Figure 1 summarizes participants’ gross motor function changes in three age groups (<72 months, 72-144 months, and 144< months). At three months post-injection, participants’ gross motor function showed statistically significant improvement in each group. Comparing the groups, the gross motor functions in lying and rolling (A) and crawling and kneeling (B) did not differ among the three groups, but gross motor functions in crawling and kneeling (B) and standing (D), walking, running, and jumping (E) differed, with the most remarkable improvement in gross motor changes at <72 months. [Figure 1 near here]. The GMFM 88 total score increased at <72 months group significantly higher than other age groups (p=0.0001, p=0.0001).

Table 3 shows the results of the repeated measures ANOVA with post-hoc analysis to assess changes in gross motor function. Standing (D) was statistically significantly improved in the <72 months group compared to other age groups [Table 3 near here].

Changes in spasticity

Figure 2 summarizes the changes in spasticity (MAS score) of the participants in three age groups. At 1- and 3 months post-injection, the participants’ spasticity in each group showed statistically significant improvement. In Figure 2A (plantar flexion of the ankle during knee flexion) and 2B (plantar flexion of the ankle during knee extension), there is no statistically significant difference (p=0.097 and 0.137) when comparing the changes in spasticity reduction between the three age groups. However,
Table 3. Post hoc analysis to determine changes in gross motor function of the participants in age groups

<table>
<thead>
<tr>
<th>GMFM-88 dimensions</th>
<th>&lt;72 vs. 72-144</th>
<th>&lt;72 vs. 144&lt;</th>
<th>72-144 vs. 144&lt;</th>
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<tbody>
<tr>
<td>Total</td>
<td>**</td>
<td>**</td>
<td>ns</td>
</tr>
<tr>
<td>Lying and rolling (A)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Crawling and kneeling (B)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Sitting (C)</td>
<td>*</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Standing (D)</td>
<td>***</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Walking, running, jumping (E)</td>
<td>ns</td>
<td>*</td>
<td>ns</td>
</tr>
</tbody>
</table>

*** - p values is <0.0001, ** - p-value is <0.001, *-p-value is <0.05, ns - Repeated measured ANOVA with Greenhouse geisser correction in gross motor function of the participants, LSD - Least significance difference test

in Figure 2C (popliteal angle), 2D (hip adductors during knee flexion), and 2E (hip adductors during knee extension), the MAS score decreased the most in the <72 months age group [Figure 2 near here].

![Figure 2. Changes in spasticity of the participants in three age groups, repeated measures ANOVA](image-url)
Table 4 showed the results of the repeated measures ANOVA with post-hoc analysis to assess changes in spasticity. Popliteal angle, hip adductor with knee flexion, and hip adductor with knee extension muscle spasticity were statistically significantly decreased in the <72 months group compared to other age groups [Table 4 near here].

Table 4. Post hoc analysis to determine Changes in spasticity of the participants in three age groups

<table>
<thead>
<tr>
<th></th>
<th>&lt;72 vs. 72-144</th>
<th>&lt;72 vs. 144&lt;</th>
<th>72-144 vs. 144&lt;</th>
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</thead>
<tbody>
<tr>
<td>a.</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>b.</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>c.</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>d.</td>
<td>**</td>
<td>*</td>
<td>ns</td>
</tr>
<tr>
<td>e.</td>
<td>**</td>
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</table>

*** - p values is <0.0001, ** - p-value is <0.001, *-p-value is <0.05, ├- Repeated measures ANOVA with Greenhouse Geiser correction in gross motor function of the participants

Discussion

The present study demonstrated that a comparison of the efficacy of BoNT-A injection between groups with different GMFCS levels (ambulant GMFCS I-III and non-ambulant IV-V) and between age groups was possible after BoNT-A injections in children with CP. Our statistical analysis revealed the following significant findings. First, the efficacy of BoNT-A injections showed substantial improvement in gross motor functions after three months when combined with physiotherapy and FES. In particular, the gross motor functions of sitting, standing, and walking improved more in children with GMFCS levels I-III. Second, spasticity management affected lower limb spasticity in all groups, significantly affecting younger children (<72 months). Our results may add to the current knowledge on optimizing spasticity management for paediatric CP rehabilitation.

Similar to the findings of previous research [21, 27-30], our study confirmed a statistically significant improvement in changes in spasticity and gross motor function due to the combined use of adjunctive therapies and BoNT-A injections. Some study results showed significantly more substantial improvement in GMFM scores when BoNT-A treatment was combined with a physical therapy program than when BoNT-A was used alone. Moreover, the international consensus statement [10] recommends adjunctive therapies following BoNT-A injections, such as physiotherapy, serial casting, and transcutaneous electrical nerve stimulation for limb hypertonicity. Besides, the latest worldwide survey [19] found that most clinicians often used physiotherapy as an adjunct, especially active exercises and stretching programs, within 30 minutes of BoNT-A injections.

In addition to the evidence on the combination of physiotherapy [27, 31], many other studies [32-35] suggested that FES should be rapidly applied to the injected muscles after BoNT-A injections.

The last systematic review has shown that BoNT-A injection is effective in reducing spasticity, improving joint range of motion, promoting gait and locomotion, and improving gross motor functions in patients with spastic cerebral palsy. The effects of BoNT-A injection can last for 3 to 6 months, and motor functions can be maintained for up to one year. However, the effectiveness of the BoNT-A injection depends on several factors, including the dose, the number of injections, and the patient’s age [36]. The younger the patient, the better the outcome. As the patient ages, the results and duration of action of botulinum toxin type A injections decrease [37]. This is because motor development in children with cerebral palsy continues until the age of 7 years [38]. Therefore, it can be assumed that children between the ages of 1 and 5 years respond best to BoNT therapy [39], and injections at an early age contribute to the development of fewer pathological gait patterns than in control groups [40,41]. One study showed that the best progress in gait and muscle tone was made in children younger than 7 years of age [42].
Botulinum toxin A injection effectively reduces spasticity and improves motor function in non-ambulatory patients with cerebral palsy. This intervention makes it possible to delay orthopedic surgery in children whose parents do not want surgery on their young child and in patients at high risk of general anesthesia [11, 29]. In general, using BoNT-A injections in children with GMFCS IV-V aims to reduce pain, prevent hip dislocations, and improve posture and support. Some studies have found a significant increase in non-ambulatory children [43]. Multilevel BoNT-A injection can be used as part of an integrated approach for focal treatment of spasticity, particularly of the hamstring and gastrocnemius muscles, in non-ambulatory young children with CP GMFCS level IV-V. Statistically significant improvement in hamstring and gastrocnemius muscle tone and improvement in knee and ankle range of motion was observed in non-ambulatory young children with CP in the 1- and three months after BoNT-A injection. This is consistent with the results of our study, in which muscle tone was reduced in children with GMFCS stage IV-V at 1 and 3 months after BoNT-A injection. Some studies need to investigate further the efficacy of BoNT-A injections in terms of functional changes at the GMFM-88 level, which corresponds to the GMFCS level [25]. The present study shows that BoNT-A injection positively affects the gross motor skills of non-ambulatory children, including lying down, rolling, crawling, and kneeling.

Several limitations of this study should be noted. First, this study was conducted at a single institution despite recruiting most of the children with CP who attended our rehabilitation clinic for BoNT-A injections. Second, the results captured only short-term spasticity management. Despite these limitations, a significant strength of our research is the use of a standardized clinical measurement tool (i.e., GMFM-88) [6] and rating scales (MAS) [26] and a relatively large sample that allowed us to describe changes in spasticity and gross motor function. Also, an independent health professional performed each measurement, and blinding was done by a third professional.

Future studies should investigate the influence of age and gross motor function level on selecting target muscles for injection.

Conclusion

We conclude that BoNT-A injection effectively improves gross motor function in patients younger than 72 months of age.

Conflict of Interest

The authors state no conflict of interest.

Acknowledgements

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References


