Effect of botulinum toxin type A (Dysport®) injection combined with rehabilitation on improving the dynamic spastic equinus foot in children with spastic cerebral palsy

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Summary

Objective: To evaluate the efficacy of botulinum toxin type A (BTA) injection in combination with rehabilitation on improving the dynamic spastic equinus foot in children with spastic cerebral palsy. *Subject and method:* Longitudinal interventional study with a control group. 140 eligible children with spastic cerebral palsy from 2 to 12 years old who were recruited from the Rehabilitation Department of National Children's Hospital from December 2015 to December 2017. *Result:* After 12 months of the treatment, the mean MAS scores of the gastrocnemius-soleus of the intervention group decreased by 1.39 ± 0.63 ($p<0.01$), and the passive ankle range of motion (ankle-PROM) was increased by 16.66 ± 11.99° ($p<0.01$), while the mean MAS scores of the control group decreased by 0.15 ± 0.34° ($p<0.01$), and ankle-PROM was increased by 3.10 ± 7.38° ($p<0.01$). The mean difference of mean MAS scores at 12 months after treating between both groups was -1.07 ($p<0.01$), and the mean difference of mean ankle-PROM was 11.69° ($p<0.01$). *Conclusion*: Botulinum toxin type A (Dysport®) - injection combined with rehabilitation improved muscles tone, increasing passive ankle range of motion, and improving on lower limb motor function in children with spastic cerebral palsy.

Keywords: Spastic cerebral palsy, botulinum toxin type A, spastic equinus foot.

1. Background

Spasticity is one of severe sequelae in children with spastic cerebral palsy (CP) leading to contraction, restriction and deformation of joints and bones, thus effecting to motor function. The spastic equinus foot is the most common deformity and often associated with spasticity of the gastric-soleus muscle complex in children with spastic CP [6]. Treatment aims to reduce the excessive plantar flexion, thereby improving gait and motor function. Botulinum toxin type A (BTA) injection and combination with rehabilitation is believed to be effective and safe for treating spasticity in children with spastic CP. BTA works to relax muscles, reduce muscles tone, and create "treatment windows" for rehabilitation, thus increasing the range of joint mobility to improve the function of standing and walking.

The BTA was first studied by Koman et al for the treatment of children with spastic CP in 1993 [2]. In Vietnam, using BTA in the treatment of muscle spasticity in children with CP has been done in a number of the Rehabilitation Centers, and has had the initial reports on the effectiveness. Therefore, we conducted this study in order to contribute more practical basis and improve the effectiveness of rehabilitation for CP children, especially those with spastic CP.

2. Subject and method

2.1. Participants

We collected 140 spastic CP children from 2 to 12 years old with standing milestone and tiptoes walking, who had been treated at the Department of Rehabilitation Medicine - National Hospital of Paediatrics from December 2015 to December 2017 and divided into 2 groups: The intervention group (n = 70) of which received rehabilitation therapy after BTA-injection and the control group (n = 70) of which received rehabilitation therapy alone. All children met the following criteria in the study:

Inclusion criteria:

Children with spastic CP has MAS score ≥ 1^+;

GMFCS levels from I - IV;

Approval for the study was obtained from all parents before enrollment.

Completed the study with total treatment follow-up duration reached 12 months.

Exclusion criteria:

Children with CP have spasticity GMFCS level V.

Severe mental retardation and/or epilepsy.

Injected botulinum toxin type A (Dysport®) or/and muscle relaxant medications and no record of surgery within 6 months prior to study participation.

Systemic infections or musculoskeletal infections at the site of treatment.

2.2. Study Design

Methods: Longitudinal intervention study with a control group.

Assessments:

Spastic sores: Using Modified Ashworth Scale (MAS), from grade 0 to grade 4 [3].

Passive range of ankle joint motion (degree°) = maximum plantarflexion plus maximum dorsiflexion. Means of assessment is a two-branch angle gauge.

We measured changes in the degree of plantarflexors spasticity by using the Modified Ashworth Scale (MAS), and in the passive ankle range of motion (PROM) at baseline and 1 month, 3 months, 6 months, 12 months after treatment.

2.3. Data processing and analysis

SPSS 18.0 software was used for statistical analysis. Statistical tests were used to

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compare the effectiveness of treatments in the 2 groups including: Chi-Square test, independent t-test, and paired t-test. The level of statistical significance was p-value less than 0.05.

3. Result

3.1. General information

Table 1. General characteristics of the research participants

Characteristics	Intervention group (n = 70)	Control group (n = 70)	Total	p
Age (month) (Mean ± SD)	60.66 ± 28.35	59.31 ± 27.24	59.99 ± 27.70	0.78
Sex (n%)				0.12
Male	47 (55.3)	38 (44.7)	85 (100)	
Female	23 (41.8)	32 (58.2)	55 (100)	
Classification (n%)				
Quadriplegia	28 (44.4)	35 (55.6)	63 (100)	0.42
Diplegia	29 (56.9)	22 (43.1)	51 (100)	
Hemiplegia (L/R)	13 (50.0)	3 (50.0)	26 (100)	

The percentage of males was majority with 60.7% (85/ 140). There was no significant difference in gender distribution between the two groups at p>0.05.

Mean age of the intervention group was 60.66 ± 28.35 months (min: 24 months - max: 144 months); the control group was 59.30 ± 27.24 months (min: 23 months - max: 141 months). There was no difference in mean age between the two groups at p>0.05.

The proportion of children with quadriplegia, diplegia and hemiplegia were 45.0%, 36.4% and 18.6% respectively. The difference in the topography between the two groups was not statistically significant at p>0.05.

3.2. Change in muscles tone after the intervention

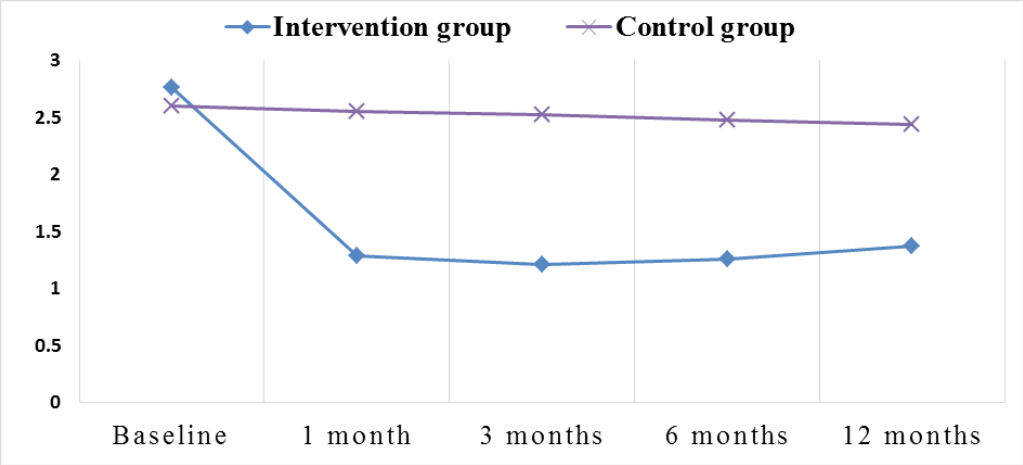
Table 2. Comparison of mean MAS scores of gastrocnemius-soleus before and after the intervention over time between the two groups

MAS score (Mean ± SD)	Gastrocnemius-soleus		Mean difference (95%CI)
	Intervention group (n = 70)	Control group (n = 70)	
Baseline	2.76 ± 0.62	2.60 ± 1.03	0.16 (-0.12; 0.45)
1 month	1.29 ± 0.50	2.55 ± 1.02	-1.26 (-1.53; -0.99)**
3 months	1.21 ± 0.46	2.52 ± 1.02	-1.31 (-1.57; -1.04)**
6 months	1.26 ± 0.46	2.48 ± 1.00	-1.22 (-1.48; -0.96)**
12 months	1.37 ± 0.50	2.44 ± 1.00	-1.07 (-1.34; -0.81)**
*Without * = p>0.05; * = p<0.05; ** = p<0.01* *Levene's Test. Independent t-test.*			

There was no difference in the mean of the ankle flexors MAS scores at baseline between the intervention group and the control group at p>0.05. The mean difference of the baseline MAS

score at all post-intervention intervals 1 month, 3 months, 6 months, and 12 months between the two groups was statistically significant at p<0.01.

There was a marked decrease in the mean MAS scores of ankle flexors in the intervention group after treating 12 months (1.37 ± 0.50) compared with the baseline (2.76 ± 0.62). The difference was statistically significant at p<0.01.



Paired t-test

Figure 1. Change in MAS sores of the gastroc-soleus muscle before and after treatment

At the time of 1 month follow-up, the reduction in MAS scores of the ankle flexion muscles in the intervention group was 1.47 compared with the baseline. The difference was statistically significant at p<0.01.

The best reduction of MAS score in ankle flexion muscles was 3 months (1.54 scores of reduction) after the BTA-injection in the intervention group. In addition, the degree of plantar flexors spasticity decreased significantly after intervening 6 months compared with the baseline (p<0.01).

The change in MAS scores of the ankle flexion muscles in the intervention group was greater in the 12th month (1.39 scores), compared to the change seen in the control group (0.15 score of reduction).

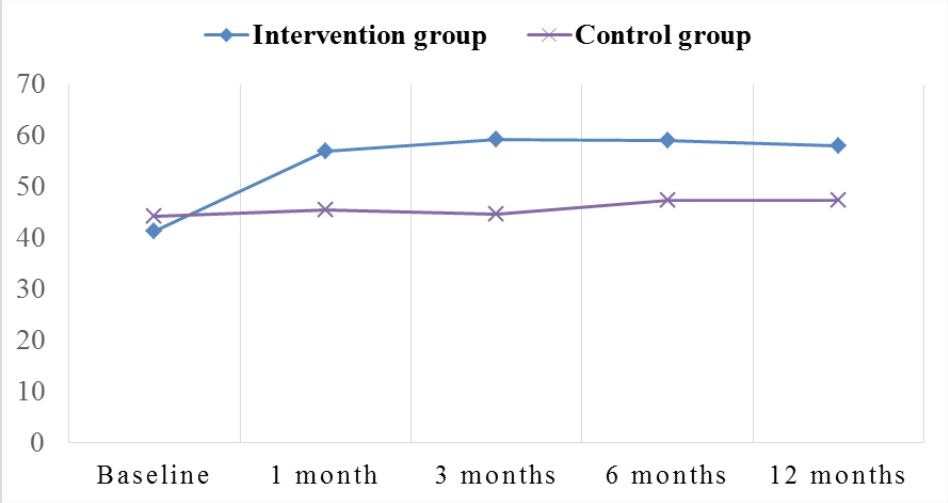
3.3. The effect on the passive range of motion after the intervention

Table 3. Comparison of the ankle-PROM before and after the intervention

Evaluation time	Ankle- PROM (degree°) (Mean ± SD)		Mean difference (95%CI)
	Intervention group (n = 70)	Control group (n = 70)	
Baseline	41.33 ± 10.46	44.21 ± 9.52	-2.87 (-6.21; 0.47)
1 month	56.95 ± 7.92	45.55 ± 7.86	11.40 (8.76; 14.04)**
3 months	59.27 ± 6.22	46.60 ± 7.40	12.66 (10.38; 14.50)**
6 months	58.98 ± 7.03	47.41 ± 6.97	11.56 (9.22; 13.90)**
12 months	57.99 ± 8.38	47.30 ± 6.80	11.69 (8.14; 13.24)**
*Without * = p>0.05; * = p<0.05; ** = p<0.01 Levene's Test. Independent t-test.*			

The mean degree of ankle-PROM at baseline between the intervention group and the control group was not significantly different at p>0.05.

There was no a statistically significant difference in the passive range of ankle joint motion at baseline between the intervention group and the control group at p>0.05. The mean difference of ankle-PROM at all post-intervention intervals 1 month, 3 months, 6 months, and 12 months compared with the baseline between the two groups was statistically significant at p<0.01.



Paired t-test

Figure 2. Change in passive range of ankle joint motion before and after treatment

The best improvement in the ankle-PROM degree was recognized at 3 months (17.94°, p<0.01) after BTA (Dysport®) injection in the intervention group, compared with the baseline. The results (Figure 2) also showed that the ankle joint angles, improved at 12 months after treatment in the intervention group were greater than the control group's (16.66°, p<0.01 versus 3.10°, p<0.01).

4. Discussion

The proportion of male children is predominant 60.7%. There was no difference in gender distribution between the intervention and control groups at p>0.05. The mean age in our study was 59.99 ± 27.77 months, which was quite similar to that of Carlos Henrique (4.73 ± 2.18 years) [4], and Lee Joung Sook et al (6.00 ± 2.70 years) [5]. The percentage of spastic CP children with quadriplegia, diplegia and hemiplegia were 45.0% (63/140), 36.4% (51/140) and 18.6% (26/140) respectively. There was no a significant difference in the spastic type of cerebral palsy between two groups at p>0.05. Distribution of topographical classification in children with CP in our study was equivalent to the results of Trinh Quang Dung and Nguyen Huu Chut [1], but different to the study results of Tedroff et al, which was 25.0% quadriplegia, 50.0% diplegia, and 22.0% hemiplegia [7].

Botulinum toxin type A (BTA) inhibits the release of acetylcholine from peripheral nerve terminals by binding to synaptic vesicles, therefore blocking neurotransmitters via the pre-synapse. Interruption of neuromuscular conduction by BTA induces a temporary weakness, which reduces focal spasticity [8]. The use of BTA to treat muscle contraction is a "treatment window" for the entire motor rehabilitation process for CP children. The results of Table 2 showed that MAS scores of the ankle flexors (gastrocnemius-soleus) between the intervention group (2.76 ± 0.62) and the control

group (2.60 ± 1.03) at baseline were not significant difference at p>0.05. This indicated a similarity in the spasticity degree of the two groups participating in the study, which allowed to compare the effect of treatment for spasticity in CP children between the intervention group and the control group.

How effectively reduce muscle spasticity was assessed on the gastroc-soleus complex in both groups of patients by comparing the mean MAS scores of ankle flexors. The results of the Table 2 showed that the improvement in the mean MAS scores of gastrocnemius-soleus in the intervention was better than the control group with a mean difference at 1 month was -1.216 (p<0.01), 3 months: -1.31 (p<0.01). The results of this study are comparable to the results of Koog and Min authors, when analyzing 15 randomized controlled trials comparing gastrocnemius-soleus muscle between BTA-injection combined with the rehabilitation group (n = 309) and the control group (n = 288) showed at 1 month after the intervention was -2.73 (p<0.01), 3 months: -1.72 (p<0.01) [9]. This difference may be due to a sharp decrease in muscle tone during the peak time of botulinum toxin type A.

We compared the efficacy of treatment at the time of the 6-month and 12-month follow-up, suggesting that the difference in the reduction of the ankle flexion muscles was maintained between the two groups (6 months: -1.22, p<0.01 versus 12 months: -1.07, p<0.01). This study result was similar to that reported by Bottos (4 months after the intervention, p=0.003; 12 months, p=0.0052) [10]. This demonstrated that in children after BTA-injection combined with physical exercise improved long-term motor function.

The Figure 1 showed that the reduction in MAS score was the best at 3 months post-injection (1.54 scores of reduction, p<0.01). The reduction of spastic ankle flexors trended to decrease after 3 months of BTA-injection and decreased significantly after 6-month to 12-month follow-ups compared with the baseline, However, the overall mean reduction in MAS score of ankle flexors at 12 months of post-intervention (1.39 scores of reduction) compared to the baseline was statistically significant difference at p<0.01.

The study also showed large variations in clinical efficacy. Our results showed that the spasticity of the gastrocnemius and soleus muscles decreased by almost 2 scores (1.54 ± 0.59, p<0.01) in the intervention group at 3 months in comparison with baseline, similar to research by Lee Joung Sook (1.30 ± 0.3, p<0.01) [5]. In contrast, in the control group demonstrated that the reduction in spasticity of ankle flexors on the MAS scale was very slow. The mean reduction of MAS scores after 1 month of rehabilitation alone was 0.04, which was not statistically significant at p>0.05. The reduction of MAS score in the control group was significant only after treatment for 3 months (p<0.05) to 6 months (p<0.01). At 12 months after treatment compared to the baseline, the ankle flexors MAS score in the control group decreased by 0.15. However, this reduction was much lower than that of children, who received BTA-injection combined with rehabilitation (1.39 sores of reduction, p<0.01).

In terms of the best MAS reduction time, the results of our study were similar to those of Trinh Quang Dung and Nguyen Huu Chut [1] but were quite different from the results of Carlos Henrique [4]. However, prolonged effects after intervention were not reported by those.

Children’s muscles, within 2 to 3 days after BTA-injection, began to weaken due to reducing muscle tone and achieved the maximum effect after 2 weeks of injection. The effect of muscle tone reduction clinically lasts for 3 to 6 months after injection, then it started to increase again. In fact, the results of our study showed that the degree of spasticity did not return to its original value after 6 months to 12

months of intervention, despite a slight increase in muscle tone after 3 months of intervention. This may be a demonstration that if physical exercise was active while the botulinum toxin type A was active and continuing to maintain rehabilitation therapy before the muscles contract back, the motor function gained can be maintained for a longer time.

The spasticity directly affects the motor impairment of children with spastic CP. Measurement of PROM is thought to be a secondary measure of defects caused by muscle contraction [8]. The greatest changes in passive motion occurred at the same time that the greatest change in the degree of contraction (MAS) was observed, which demonstrated that the muscle tone affects the range of motion at one joint. Therefore, we use a passive ankle-PROM measurement as a research indicator to evaluate the effect of ankle muscle contraction reduction.

At baseline, the results of Table 3 showed that the passive ankle joint mobility between the two groups was no statistically significant at $p>0.05$.

The mean degree of ankle-PROM of the intervention group, and the control group at the 1-month, 3-month, 6-month and 12-month follow-ups were improved. The improvement of passive ankle mobility among children with BTA-injection combined with rehabilitation at all times was better and faster than that of children with rehabilitation alone (control group). This difference was statistically significant at $p<0.01$. This result showed the good effect of the rehabilitation program for all participants.

The results of Figure 2 illustrated the best improvement of ankle-PROM was 17.94° at 3 months after BTA-injection in the intervention group compared with the baseline. The difference was statistically significant at $p<0.01$. Ankle-PROM continued to improve after 6 months of treatment (17.64°, $p<0.01$) in the intervention group, followed by a tapering trend. By the time of 12 months, it was close to the baseline, but the difference was statistically significant at $p<0.01$. This was quite reasonable when compared to the variation in the ankle-PROM over time (Figure 2) with the reduction of the ankle MAS scores. In our opinion, the ankle-PROM were still improved because the children had been practicing continuously during the time when there was no contraction. This is another evidence that confirms the sustainability of BTA-injection in combination with rehabilitation.

Increased stretched reflex and spasticity can cause shortening of the muscles, eventually leading to contraction, and reduction of joint mobility [7]. Therefore, good treatment will help avoid this consequence. The combination of BTA-injection with rehabilitation therapy showed a good improvement in the reduction of spasticity, increased joint mobility for children with spastic cerebral palsy. In addition, these improvements are thought to be directly related to motor function (GMFCS) following injection of BTA in combination with rehabilitation therapy for spastic cerebral palsy.

5. Conclusion

Efficacy of reduced muscle spasticity, improved passive joint mobility at 3 months after botulinum toxin type A (Dysport) injection combined with rehabilitation therapy achieved, maintained for 12 months ($p<0.01$).

Botulinum toxin type A (Dysport) injection combined with rehabilitation improved muscle tone, increasing passive ankle range of motion, and improving on lower limb motor function in children with spastic cerebral palsy.

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