Effect of botulinum toxin type A (Dysport®) injection combined with rehabilitation on gross motor function in children with spastic cerebral palsy

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Summary

Objective: To evaluate the effect of botulinum toxin type A (BTA) injection in combination with rehabilitation on gross motor function in children with spastic type of cerebral palsy. *Subject and method:* Longitudinal intervention study with a control group. 140 eligible children with spastic cerebral palsy from 2 to 12 years old were recruited from the Rehabilitation Department of National Children's Hospital from December 2015 to December 2017, and divided into two groups in our study. *Result and conclusion:* After 12 months of intervention, the mean of GMFCS scores in the study group decreased by 0.87 ± 0.56 ($p<0.01$). The mean scores in the control group decreased by 0.31 ± 0.47 ($p<0.01$). The mean difference of mean GMFCS scores after the intervention between the two group was 0.48 ($p<0.001$). Children with spastic cerebral palsy, who received BTA-injection in combination with rehabilitation achieved good and very good improvement which was 7.36 times higher than children who had only rehabilitation therapy ($p<0.001$).

Keywords: Spastic cerebral palsy, botulinum toxin type A, gross motor function.

1. Background

The overall cerebral palsy rate ranges from 1/1.000 to 3/1.000 live births in which spastic cerebral palsy accounts for 62.6% to 65.0% [1]. Spasticity in the cerebral palsy limits the movement of the joints, leading to muscle contraction and stiffness, which severely affect he motor function, development and daily life of the child. Worldwide, use of botulinum toxin type A to reduce muscle tone, support for other rehabilitation interventions has been made since 1993 [5].

In Vietnam, there have been some reports of supportive effects as well as the safety of BTA in spastic cerebral palsy, but the majority of these reports were evaluated on small samples and short study time [2], [3]. Based on this fact, we conducted this study to evaluate the effect of BTA (Dysport®) injection combined with rehabilitation on gross motor function in children with spastic cerebral palsy.

2. Subject and method

2.1. Participants

140 eligible children with cerebral palsy from 2 to 12 years old with GMFCS level II, III, and IV

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were recruited from the Rehabilitation Department of National Children's Hospital from December 2015 to December 2017 and divided into 2 groups: The intervention group (n = 70) of which received rehabilitation therapy after botulinum toxin type A injection and the control group (n = 70) of which received rehabilitation therapy alone.

2.2. Method

Methods: Longitudinal interventional study with a control group.

Assessments:

The gross motor function of cerebral palsy was assessed by Gross Motor Function Classification Scale (GMFCS) with 5 levels before and after intervention [6]. We measured the changes in the GMFCS levels at baseline and 1 month, 3 months, 6 months, 12 months after treatment.

Criteria for scoring and classifying the level of progress after intervention:

Table 1. Scoring criteria

Gross motor function level - GMFCS	Score
Level I	1
Level II	2
Level III	3
Level IV	4
Level V	5
Progressive GMFCS scores = Scores before intervention - Scores after intervention	

Table 2. Progress level classification

Level of progress	Progressive score
Worsening	< 0
No progress	0
Good progress	1
Very good progress	≥ 2

2.3. Data processing and analysis

SPSS 18.0 software was used for statistical analysis. Statistical tests were paired t-test, independent t-test, and Fisher's Exact. The level of statistical significance was p-value less than 0.05.

3. Result

3.1. General information

Males made up the majority 60.7% (85/140). There was no difference in gender distribution between the intervention group and the control group (p>0.05).

Mean age of the intervention group was 60.66 ± 28.35 months (min: 24 months - max: 144 months) and the control group was 59.3 ± 27.24 months (min: 24 months - max: 132 months). Mean age of both groups was 59.99 ± 27.77 months (min: 24 months - max: 144 months). There was no significant difference in the mean age between the two groups at p>0.05. 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.

The mean of GMFCS scores of two groups at baseline was 2.58 ± 0.66. The mean of GMFCS scores in the intervention group was 2.61 ± 0.67, and in the control group was 2.54 ± 0.65. There was no significant difference in mean of GMFCS score at baseline between the two groups (p>0.05).

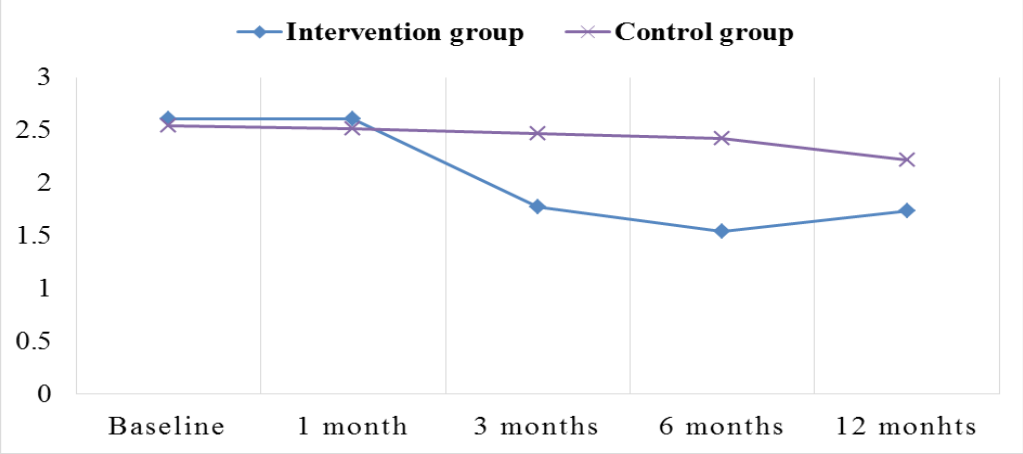
3.2. The results

Table 3. Comparison of mean gross motor function scores (GMFCS) before and after intervention between the two groups

Evaluated interval	GMFCS (Mean ± SD)		Mean difference (95%CI)
	Intervention group (n = 70)	Control group (n = 70)	
Baseline	2.61 ± 0.67	2.54 ± 0.65	0.07 (-0.15, 0.30)
1 month	2.57 ± 0.71	2.51 ± 0.70	0.06 (-0.17, 0.29)
3 months	1.77 ± 0.74	2.47 ± 0.72	-0.70 (-0.94, - 0.45)**
6 months	1.54 ± 0.73	2.42 ± 0.73	-0.88 (-1.13, - 0.64)**
12 months	1.74 ± 0.97	2.22 ± 0.91	-0.48 (-0.80, - 0.16)**
Without = p>0.05, *= p<0.05, **= p<0.01, Levene's Test. Independent t-test*			

There was no difference in the mean of GMFCS scores between the intervention group and the control group at baseline and 1 month after intervening (p>0.05).

There was a difference in the mean of GMFCS scores at 3, 6 and 12 months after treatment between study and the control group at p<0.01.



Paired t- test.

Figure 1. Comparison of the mean GMFCS scores over time in each group

After 1 month of the intervention, the mean of GMFCS scores in the intervention group decreased by 0.04 and in the control group decreased by 0.03. This difference was not statistically significant in both groups.

After 3 months of the intervention, the mean of GMFCS scores in the intervention group decreased by 0.84 (p<0.01), and in the control group was 0.07, compared to baseline (p<0.05). The mean of GMFCS scores in the intervention group were 12 times lower than those in the control group after treatment. At 6 months after the intervention from baseline, the mean of GMFCS scores in the intervention group decreased by 1.07 versus 0.11 in the control group respectively. The difference was statistically significant at p<0.05. Mean scores in the intervention group were 9.7 times lower than those in the control group.

After 12 months of the intervention, the mean of GMFCS scores in the intervention group was 0.87 (p<0.01), and in the control group was 0.31 (p<0.01). Mean scores in the intervention group

decreased more than 2.8 times compared to the control group.

In the intervention group, the mean decrease of GMFCS was greatest at 6 months after the intervention (1.07, p<0.01), in the control group the greatest decrease at 12 months after the intervention (0.31, p<0.01).

Table 4. Distribution of the progressive GMFCS scores post-treatment

Progression level	n	Percentage (%)
No progress	64	45.7
Good and very good progress	76	54.3
Total	140	100

The percentage of children with spastic cerebral palsy improved well and very well after the treatment was 54.3%.

Table 3. Relationship between progressive level and the intervention

Group	Progression level		Total (%)	OR (95%CI)	p
	Good and very good	No progress			
Intervention group (n = 70)	54 (77.1)	16 (22.9)	70 (100)	7.36 (3.47, 15.62)	0.001
Control group (n = 70)	22 (31.4)	48 (68.6)	70 (100)		
Total	76 (54.3)	64 (45.7)	140 (100)		
Fisher's Exact test					

The children who received botulinum toxin type A (Dysport®)-injection combined with rehabilitation therapy showed a progressive improvement in gross motor function of 7.36 times higher than those with rehabilitation alone, which was statistically significant at p<0.01.

4. Discussion

The mean age in our study was 59.99 ± 27.77 months, lower in Carlos Henrique's study (4.73 ± 2.18 years) [7]. Male occupancy was 60.7%, similar to that of Carlos Henrique author [7]. The proportion of children with quadriplegia was 45.0% (63/140), diplegia was 36.4% (51/140) and hemiplegia was 18.6% (26 /140).

At baseline, the mean of GMFCS scores in both groups were not statistically significant different (the intervention group 2.61 ± 0.67, the control group 2.54 ± 0.65). At 1 month follow-up, the mean of GMFCS scores in both groups decreased, however, it was not significant (the intervention group 2.57 ± 0.71; the control group 2.51 ± 0.70). This may be due to 2 weeks of fixed castings after BTA-injection, the children suffered from inactive pain so they were not active enough after removing the powder.

After 3 months of the intervention, the mean of GMFCS scores in the intervention group decreased by 1.77 ± 0.74 and the control group was 2.47 ± 0.72. The difference gap in the mean of GMFCS scores between two group was 0.7 (p<0.01). This may be due to the decrease of muscle tone after BTA-injection combined with physical exercise made the children's gross motor function better. Particularly, the gastrocnemius and soleus were stretched, the mobility of the ankle joints is less restricted, so children's balance of standing and walking was

better, children were more likely to walk and less lose strength.

The 6-month follow-up of the intervention group showed that mean of GMFCS scores continued to decrease (1.54 ± 0.73). For the control group, the mean score was lower but still higher than the study group (2.42 ± 0.73). The difference gap in mean scores between two groups was 0.88, and it was statistically significant at p<0.01.

After 12 months of the intervention, the mean of GMFCS scores in the intervention group was increased from 1.54 ± 0.73 up to 1.74 ± 0.97. This is appropriate because, according to studies in the world, the effects of BTA-injection last for 3 to 6 months, after which the effect of the drug is gone, the muscles tone of the children begin to increase again. Thus, children are more difficult to exercise [3]. However, after 12 months of intervention, the mean of GMFCS scores in the intervention group was still lower than in the control group (1.74 ± 0.97, p<0.01 versus 2.22 ± 0.9, p<0.01) and this difference was significant at p<0.01. This is evidence for the long-term effects of BTA-injection combined with rehabilitation therapy.

In our study, the mean difference of GMFCS scores between baseline and post-intervention periods was highest at 6 months (1.07 ± 0.51, p<0.01), followed by 12-month follow-up (0.87 ± 0.56, p<0.01). This showed that if children physical exercise aggressively during the effective time of the drug and continue to exercise after the drug were no longer effective, the motor function gained can be sustained over a longer period of time. This is an another evidence that confirms the sustainability of BTA-injection in combination with rehabilitation.

The rate of general improvement on gross motor function after intervening was 54.3% (76 children). The rate of improvement at good and very good level in the study group was 77.1% (54/70), in the control group was 31.4% (22/70). The rate of good and very good progress in the intervention group were higher than those in the study by Trinh Quang Dung and Nguyen Huu Chut authors. This may be due to the fact that our study was conducted after the study by Trinh Quang Dung and Nguyen Huu Chut, when the BTA-injection procedures and rehabilitation practices were improved. However, the rate of no progress in our study was also higher in the study of Trinh Quang Dung and Nguyen Huu Chut. This may be due to longer duration of evaluation in our study (12 months), when the effects of the drug had run out 6 months earlier. In contrast, the study of Trinh Quang Dung and Nguyen Huu Chut, the time of evaluation was at the end of botulinum toxin type A effects [2].

When analysing the relationship showed that if children with cerebral palsy are given BTA-injection in combination with rehabilitation, the ability to progress at a good and very good level is 7.36 times higher than that of children who practice only rehabilitation, statistically significant at p<0.001.

5. Conclusion

After 12 months of the intervention, the mean GMFCS scores in the intervention group decreased by 0.87 ± 0.56, p<0.01. The mean scores in the control group decreased by 0.31 ± 0.47, p<0.01. The mean difference of mean GMFCS scores after the intervention between two groups was 0.48, statistically significant at p<0.001.

Children with spastic cerebral palsy who received BTA-injection in combination with rehabilitation were able to progress at a good and very good level 7.36 times higher than that of those who had rehabilitation therapy alone with statistical significance at p<0.001.

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