

## **Injection Frequency of Botulinum Toxin A for Spastic Equinus – A Randomised Clinical Trial**

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## Abstract

### Aim

We compared two Botulinum toxin A (BoNT-A) injection frequency regimens, 12-monthly versus 4-monthly, for spastic equinus in a randomised clinical trial. The primary outcome measure was passive ankle dorsiflexion.

### Method

Forty-two ambulant children with spastic equinus, secondary to cerebral palsy, mean age 3 years 6 months (SD 13 months) were randomised to receive either 12-monthly or 4-monthly BoNT-A injections to the calf, over a 26-month period. Twenty-one children had spastic hemiplegia, 21 children had spastic diplegia. A fixed 6U/Kg dose of Botox® was injected into the gastrocnemius muscle of both limbs in children with diplegia and the gastrocsoleus of the affected limb in children with hemiplegia, under mask anaesthesia.

### Results

Forty-two children entered the trial with 21 subjects randomised to each group. There were three withdrawals, and two children received serial casting midway through the trial. There was no significant difference in passive dorsiflexion between 12-monthly and 4-monthly regimens ( $p=0.41$ ). There were also no significant between group differences on secondary outcome measures. There were no serious adverse events, the rate was 1.2 adverse events/child/year in the 12-monthly group and 2.2 adverse events/child/year in the 4-monthly group. Subgroup analysis revealed a significant difference in passive dorsiflexion between children with hemiplegia and diplegia ( $p=0.01$ ).

### Interpretation

There was no significant difference between 12-monthly and 4-monthly injection regimens on passive dorsiflexion or secondary outcome measures. BoNT-A injections for spastic equinus may be recommended on a 12-monthly basis.

### What this paper adds

- Injecting of BoNT-A once each year was as effective as injecting three times per year, for young children with cerebral palsy and spastic equinus.
- Children with spastic hemiplegia had different responses to those with spastic diplegia.
- Injections of BoNT-A for spastic equinus may be recommended on a 12-monthly basis.

### Level of Evidence

Level I: Prospective, parallel-group randomised clinical trial.

**Key words** spastic equinus, cerebral palsy, botulinum toxin A, RCT.

### Shortened form of title:

Injection frequency for spastic equinus.

Equinus is the most common gait abnormality affecting children with cerebral palsy (CP)<sup>1</sup>. Calf spasticity increases until the age of four years and then decreases until age 12 years, during which time many children develop a fixed contracture<sup>2</sup>. In the Swedish CP-UP study, this was associated with a 19° reduction in the mean range of ankle dorsiflexion between birth and age 18 years<sup>3,4</sup>. In children with CP, muscles are shorter with reduced volume, cross-sectional area and muscle thickness<sup>5</sup>. During the early childhood phase of spastic equinus, calf lengthening surgery may be unpredictable<sup>6</sup> and non-operative methods for maintaining muscle length are often preferred.

Injection of Botulinum toxin-A (BoNT-A) for spastic equinus produces a dose-dependent partial chemodenervation resulting in reduced muscular activity for approximately 12-16 weeks<sup>7</sup>. Reduction in tone and spastic reflexes permits increased passive stretch, which has been assumed to increase muscle growth<sup>7</sup>. In juvenile hereditary spastic mice, injection of BoNT-A prevented equinus contracture<sup>8</sup>. However, this has not been replicated in children with CP, most likely attributable to the longer growth period. In one clinical study of children with spastic equinus, injection of the gastrocnemius with BoNT-A resulted in gastrocnemius lengthening for 24 weeks<sup>9</sup>.

Reasonable evidence and consensus exists regarding the dose of BoNT-A injection to the gastrocnemius, for the management of spastic equinus<sup>7,10</sup>. In one dose-ranging study, intermediate doses produced the best response for muscle length during gait<sup>11</sup>. An optimal dose exists, above which the benefits declined, probably related to spread of BoNT-A to adjacent muscles and the effects of generalised weakness.

In ambulant children, GMFCS I-III, injection of BoNT-A in accepted doses is usually well tolerated and relatively safe<sup>7,12</sup>. A Cochrane review of three published randomised controlled trials (RCTs) found the evidence for BoNT-A in the management of leg spasticity was not strong<sup>14</sup>. A systematic review of eight RCTs found moderate evidence in support of the use of BoNT-A combined with usual care or physiotherapy for children with CP<sup>15</sup>. In a systematic review, BoNT-A was reported to increase ankle dorsiflexion range<sup>16</sup>.

Injection of BoNT-A for spastic equinus fails in some children<sup>17</sup>. Unresponsiveness can be primary when it fails the first time, or secondary when it is initially successful but fails after subsequent injections<sup>7</sup>. Although secondary unresponsiveness has been correlated with neutralising antibody (NAB) formation, the presence of NAB without treatment failure may be more frequent than therapy failure due to NAB<sup>7,17</sup>. Patient-based testing of motor function is an alternative method for detecting the presence of secondary unresponsiveness<sup>7</sup>.

In contrast to the consensus and evidence about dose<sup>7,10</sup>, no consensus and little evidence exists about injection frequency for spastic equinus in children with CP. In the only injection frequency RCT published to date, Kanovský and colleagues were unable to detect a significant difference between 12 monthly and 4 monthly injections over a two-year period<sup>13</sup>. This was a large study with well-accepted outcome measures, including ankle dorsiflexion by standard goniometry and the Gross Motor Function Measure<sup>13</sup>.

Elsewhere in the literature, recommendations regarding injection intervals range between three and 12 months, based largely upon factors such as clinical intuition, avoidance of antibody formation, convenience, and cost<sup>7,9,10</sup>. Prescribing information supplied with Botox® (Allergan Pharmaceuticals) does not include evidence-based recommendations for frequency of treatment to the lower limbs in children with cerebral palsy. Establishing optimal frequency of BoNT-A treatment could be of considerable benefit to patients, service providers and health care economists. An essential part of the scientific method is to replicate

novel studies. The primary aim of this study was therefore to investigate the optimal frequency of BoNT-A injections for the treatment of spastic equinus, using similar injection regimens but with different outcome measures<sup>13</sup>.

The International Classification of Functioning, Disability and Health (ICF) model from the World Health Organization was used to guide selection of outcome measures. The primary outcome measure was passive dorsiflexion with the knee extended, a proxy measure for the length of the gastrocnemius muscle-tendon unit. Secondary outcome measures were motor responsiveness, functional mobility and child health-related quality of life<sup>18</sup>. The primary hypothesis to be tested was:

1. Ambulant children with spastic equinus, who receive 4-monthly BoNT-A injections will have greater passive ankle dorsiflexion after two years than children receiving 12-monthly injections.

Secondary aims were to study:

2. a) Differences in motor responsiveness to BoNT-A injections between the two groups at the end of the clinical trial.
- b) Differences in function or health-related quality of life between the two groups.

## Method

### Trial Design, Ethical Approval and Study Funding

Ethical approval was given by each institution's Human Research and Ethics Committee (Royal Children's Hospital: 27062C, Monash Children's Hospital: 07083C). Written, informed consent was obtained from the parents of all children prior to study inclusion. The reporting in this trial follows the CONSORT guidelines.

This was a two-centre, 26 month, prospective, parallel-group RCT comparing two injection frequencies of BoNT-A injections for spastic equinus. The trial was entered on the Australia and New Zealand Clinical Trials Registry (No. 12607000326493) and funded by the Australian National Health and Medical Research Council (Grant No. 454705). No pharmaceutical company sponsorship was received in support of this clinical trial.

### Participants

Inclusion criteria were spastic equinus defined as the absence of heel contact during the stance phase of gait, a diagnosis of spastic CP, toxin naïve, age 2-5 years, GMFCS levels I-III and greater than 5° passive dorsiflexion in subtalar neutral with the knee extended<sup>19</sup>. Exclusion criteria were lack of consent, previous surgery, contraindications to BoNT-A or use of medications that could potentially interact with BoNT-A. The study took place at two tertiary paediatric hospitals between December 2007 and October 2012. Children referred for BoNT-A spasticity management at both hospitals were screened for trial eligibility and invited to participate by the study coordinator (TH-I).

### Interventions

The calf muscle was injected with a fixed dose of Botox® (Allergan Pharmaceuticals Inc. Irvine, CA) 6U/kg body weight at a fixed dilution of 100U in 4.0ml of normal saline. Injections were guided by electrical stimulation under mask anaesthesia, to two sites in the medial belly and one site in the lateral belly of the gastrocnemius<sup>7</sup>. Children with spastic

diplegia had injections to the gastrocnemius muscle in both lower limbs at a dose of 6U/kg, a total dose of 12U/kg. Children with spastic hemiplegia had injection of the gastrocnemius and soleus muscles on the affected side<sup>7</sup>, at a dose of 6U/kg. The maximum total dose was fixed at 18U/kg body weight with the difference between the calf muscle dose and total dose available for use at other sites, according to clinical indication. Children in both groups were reviewed every four months by the study co-ordinator to standardise care, including use of ankle-foot orthoses and access to post-injection physiotherapy.

### **Primary Outcome Measure**

Passive ankle dorsiflexion at baseline and 26-months was performed under mask anaesthesia by an assessor blinded to group allocation. Measurement was performed immediately prior to injection, using a precise and reliable method with standard error of measurement 3.9° SD 2.0; 95% CI 3.3, 4.0 which has been fully described previously<sup>20</sup>. The applied torque was standardised to 50% body weight, with a digital photograph taken and software used to measure passive dorsiflexion<sup>20</sup>.

### **Secondary Outcome Measures**

1. Motor responsiveness to BoNT-A: a three-dimensional gait analysis (3DGA) was performed two weeks before and four weeks after the final BoNT-A injection. Maximum ankle dorsiflexion was recorded, between 30 and 35% of the gait cycle.
2. Functional Mobility: at baseline and 26-months, the Functional Mobility Scale (FMS) was completed by an assessor blinded to group allocation, and the Gillette Functional Assessment Questionnaire (FAQ) was completed by the child's parent or usual carer<sup>21,22</sup>.
3. Health-Related Quality of Life (HRQoL): at baseline and 26-months, the Child Health Questionnaire (CHQ) was completed by the child's parent or usual carer<sup>18,23</sup>.
4. The incidence of Adverse Events (AEs) due to BoNT-A injection and other factors such as fasting or mask anaesthesia, were recorded. AEs were recorded by the study co-ordinator at clinical review or by interview, within 10 days of each injection episode or at next clinical review. A serious adverse drug reaction was defined as death, a life-threatening adverse experience, hospitalisation or a persistent or significant disability/incapacity. Other AEs were classified as mild if no intervention was required, or moderate if medical advice or assessment was sought.

### **Subgroup Analyses**

Additional subgroup analyses were performed to determine any difference in passive dorsiflexion within and between children with hemiplegia and diplegia over the 26-month period.

### **Sample Size Calculation**

The study was powered to detect a 5° difference in range with 90% power and 0.05% confidence on the assumption of a standard deviation of 5°, which equates to a large effect size of 1. On this basis, 21 participants were required in each group. The aim was to recruit 30 subjects per group to allow for potential withdrawals from the study.

### **Randomisation**

Participants were screened for eligibility and enrolled into the study by the study coordinator. Following enrolment, participants were randomised to either 12-monthly or 4-monthly BoNT-A injection groups using a minimisation approach. This allowed even distribution between the two groups for potential confounding factors of CP subtype (diplegia, hemiplegia), GMFCS level and whether muscles other than the calf required injection over the projected 26-month period. The random allocation sequence was computer-generated by a statistician at a remote location after receiving an email from the study coordinator containing subject number and details for minimisation. The statistician then emailed the study coordinator with group allocation, who in turn informed the subject and family at the first injection session.

## **Blinding**

It was not possible to blind children, parents or injectors to group allocation. However, outcome assessors and clinical analysts were blinded to group allocation.

## **Statistical Methods**

All outcome data were screened for outliers and normality of distribution, with no significant departures found. Linear regression equations were performed for passive dorsiflexion, motor responsiveness and HRQoL outcomes. Confidence intervals were calculated with robust standard errors to allow for excess correlation in measuring different legs from the same patient. Passive dorsiflexion was additionally reported as change from baseline to assist in clinical interpretation. These change values were derived from the average of the differences between final (26-month) and baseline dorsiflexion measures, with a t-test to determine the standard error and confidence intervals. Functional mobility (FMS and FAQ) was analysed using the Wilcoxon rank sum test. Effect size was calculated using Cohen's  $d$ <sup>24</sup>. All analyses were performed by intention-to-treat, with all statistical tests two-sided and the significance level set at  $p=0.05$ . Statistical analyses were performed using Stata® Release 13 statistical software (StataCorp LP College Station Texas).

## **Results**

### **Study recruitment, randomisation and numbers analysed: Figure 1 CONSORT**

Enrolment was slower than expected and ceased after 42 children entered the trial. One child with hemiplegia was withdrawn from the 12-monthly group at the first 4-month review due to rapid progression to fixed contracture. In the 4-monthly group, two children were withdrawn; one (hemiplegia) by parents due to burden of care associated with unstable epilepsy and the other (diplegia) by the treating physician having assessed the trial protocol as not meeting the clinical needs of the child. Two children in the 12-monthly group did not complete the final gait analysis to determine motor responsiveness. There were no other missing data. In the 4-monthly group, two children with hemiplegia developed fixed contracture during the trial and were managed mid-trial by serial casting. No other children received casting during the trial period. These children were included in the intention-to-treat analyses. Nineteen children in the 4-monthly group (90%) and 20 in the 12-monthly group (95%) completed the trial protocol.

### **Baseline Data: Table I**

The groups were similar on all criteria, including the use of AFOs and access to post injection physiotherapy.

## Primary outcome measure: Ankle Dorsiflexion: Table II

Both groups maintained passive ankle dorsiflexion and there was no significant difference from baseline to 26-months between the 12-monthly and 4-monthly injection groups (3.3° greater in 12-monthly group 95% CI -4.7, 11.2  $p=0.41$ ). The effect size was small: 0.15 (95% CI 0.36, 0.66). The difference in mean passive dorsiflexion change was 2.0° (95% CI -5.0, 9.1) between injection frequency groups.

## Secondary outcome measures: Table III and Figure 2

Both injection frequency groups demonstrated motor responsiveness to the final injection of BoNT-A, demonstrated by increased dorsiflexion during stance, with no significant between group differences ( $p=0.19$ , Table III).

The FMS 50m and the FAQ additional activities score were slightly better in the 4-monthly group than in the 12-monthly group but this was not significant. No significant differences were found for the FMS 5m or 500m distances (Fig. 2A) or functional level within the FAQ (Fig. 2B). There were no significant between group differences for any of the 13 domains of the CHQ.

## Adverse Events: Table IV

There were no serious adverse events. The incidence of mild and moderate AEs per injection was similar between groups, however children in the 4-monthly group had twice the number of AEs. The most common AEs were ‘flu-like’ illnesses, localised muscle pain, and falls. Two children attended the Emergency Department on the evening of BoNT-A injection. One child had a dose of medication for epilepsy omitted, whilst fasting for injection of BoNT-A and presented with seizures. The other child presented with post injection vomiting.

## Subgroup analyses: Table V

Children with hemiplegia had much less passive dorsiflexion than children with diplegia, regardless of injection frequency ( $p=0.01$ ). The effect size was large for CP subtype: 0.80 (95% CI 0.24, 1.37). Children with hemiplegia lost an average 8.5° passive dorsiflexion whilst those with diplegia gained an average 1.6° over the 26-month study period. There was no significant difference from baseline to 26-months when injection frequency was analysed for children with hemiplegia ( $p=0.82$ ) or for children with diplegia ( $p=0.39$ ).

## Discussion

Injection of BoNT-A for spastic equinus every four months did not confer any advantage over injections every 12 months, for the cohort as a whole, similar to the findings by Kanovský and colleagues<sup>13</sup>. However, both injection groups maintained passive dorsiflexion over the two-year study period. This may indicate a benefit over the expected natural history but this is impossible to prove without a control group<sup>4</sup>. We had both ethical and practical concerns regarding the inclusion of a “no treatment” control group. We found no significant differences in functional mobility, motor responsiveness or child health-related quality of life, suggesting a small treatment effect size and that neither group was disadvantaged. The rate of adverse events was similar between groups and consistent with previous studies<sup>11-13</sup>. An additional confounder in the study was the variable use of concomitant injection of the medial hamstrings, particularly in children with diplegia. This was permitted under study conditions to reflect patient, family and injector preferences. The expected effect would be to improve knee extension by a reduction in “apparent equinus”.

New findings, specific to this study relate to the sub-group analyses (Table V). A large effect size was seen for the significant difference in passive dorsiflexion between children with hemiplegia and children with diplegia, regardless of injection frequency. These findings provide important new information to guide injection protocols in children with hemiplegia compared to those with diplegia.

For all children with hemiplegia, there was a mean  $8.5^{\circ}$  loss of passive dorsiflexion over the course of study. There are anecdotal reports that children with hemiplegia progress to fixed contracture more quickly than those with diplegia<sup>7</sup>. The response by many clinicians when faced by no response to injection, is to increase the frequency of BoNT-A injections. However, this may be the wrong strategy based on our results. In children with hemiplegia, the loss of passive dorsiflexion was  $9.0^{\circ}$  over the 26-month period for those receiving 4-monthly injections, compared to  $8.1^{\circ}$  for those undergoing injections every 12-months (Table V). Tripling the frequency of injection does not prevent progressive contracture in children with hemiplegia. Our recommendations are to assess the response on an individual basis and cease injections of BoNT-A when fixed contracture develops, with early referral for surgical lengthening of the fixed contracture.

Unlike children with hemiplegia, there were important differences for injection frequency in children with diplegia. For children with diplegia as a whole, mean passive dorsiflexion increased from  $7.7^{\circ}$  to  $9.9^{\circ}$  at 26-months (Table V). Children with diplegia receiving 12-monthly injections maintained their range of passive dorsiflexion, which increased slightly from  $6.6^{\circ}$  to  $7.5^{\circ}$ . However, those undergoing 4-monthly injections had increased passive dorsiflexion from  $8.7^{\circ}$  to  $12.4^{\circ}$ . For some children with diplegia and muscle weakness, the increase in ankle dorsiflexion was excessive when individual gait studies were reviewed. In these children, increased ankle dorsiflexion was achieved at the cost of increased knee flexion, a most undesirable outcome<sup>1,6</sup>.

In children with hemiplegia, lower limb involvement is more pronounced distally than proximally and crouch gait is unknown<sup>6</sup>. In children with diplegia, the knee, not the ankle is the problem level and crouch gait, as part of natural history or the result of intervention, is very common<sup>1,6</sup>. Mild equinus may help direct the ground reaction force in front of the knee, providing protective coupling and knee extension. We conclude that the frequency of injection in children with diplegia should be once every 12 months. More frequent injections may result in longer, weaker, incompetent gastrocsoleus muscles, predisposing the child to the development of crouch gait. In children with diplegia, “a little equinus is better than calcaneus”<sup>6</sup>.

In conclusion, our study-based treatment recommendations are for 12-monthly injections for the management of spastic equinus in children with hemiplegia and children with diplegia. Children with hemiplegia do not benefit from increased frequency of injections. The progression to fixed contracture occurs early in childhood and is not amenable to increased injection frequency. Emerging evidence from animal studies suggests that repeated BoNT-A injection before full muscle recovery may lead to dramatically increased reductions in muscle torque, and pathological changes within skeletal muscle including fibrosis and fatty infiltration<sup>25</sup>. For children with diplegia, increased injection frequency may achieve “foot flat” which is often regarded by parents and clinicians as a good outcome. However foot flat and dorsiflexion even within the “normal range” may increase the risk of crouch gait. In ambulant children with CP, a 12-monthly injection regimen will offer the same degree of efficacy, fewer adverse events, and greater protection against crouch gait



compared with more frequent injections. This will result in substantial savings at a time of spiraling healthcare costs.

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Table I: Baseline demographic and clinical characteristics of the study cohort.

<b>Baseline Characteristics*</b>		<b>12-monthly group n=21</b>	<b>4-monthly group n=21</b>
Age years, months (SD)		3y 5m (SD 1y 1m)	3y 5m (SD 1y 2m)
Gender	Male	13	10
	Female	8	11
CP Classification	Hemiplegia	11	10
	Diplegia	10	11
GMFCS	Level I	11	9
	Level II	8	11
	Level III	2	1
Randomised to receive calf + other muscle injections		13	16
Usual care: orthotics	Solid AFO	14	16
	Hinged AFO	15	12
	In-shoe orthotic	2	0
Usual care: physiotherapy		Matched funding: equal post injection therapy available to both groups	

\* There were no significant differences in baseline characteristics between the two groups

Table II: Ankle dorsiflexion for injection frequency groups

Passive Dorsiflexion	Baseline		26 months		Change		Mean difference between groups at 26mths	95% CI	<i>p</i>
	Mean	SD	Mean	SD	Mean	SD			
12-monthly	7.4°	12.8°	5.3°	14.3°	-2.7°	14.1°	3.3°	-4.7°, 11.2°	0.41
4-monthly	8.3°	9.4°	8.6°	9.3°	-0.7°	12.7°			
Difference: mean 95% CI					2.0°	-5.0°, 9.1°			

Negative (-) values for change scores indicate a loss of mean dorsiflexion range; positive (+) values indicate a gain in mean dorsiflexion range. The change scores may not reflect the apparent difference between baseline and 26 months due to some missing data at follow-up.

Table III: Motor responsiveness to Botulinum toxin-A: Maximum ankle dorsiflexion from 3DGA

Motor responsiveness to BoNT-A	12-monthly injection group mean (SD)		4-monthly injection group mean (SD)		Mean difference between groups*	95% CI	<i>p</i>
	Pre-injection	Post-injection	Pre-injection	Post-injection			
Maximum ankle dorsiflexion (°)	-4.6° (17.9)	+3.2° (17.0)	+3.9° (13.4)	+10.0° (10.8)	6.8°	-3.4, 17.0	0.19

Negative (-) values indicate equinus; positive (+) values indicate dorsiflexion.

Table IV: Adverse Events

Adverse events	12-monthly	4-monthly
	Total injection episodes = 61	Total injection episodes = 140
Injection episodes associated with 1 or more mild-moderate AEs	26	47
Injection episodes with no AEs	35	93
Mild-moderate AE rate per injection episode	43%	34%
AE per child per year of treatment*	1.2	2.2
Total mean dose per injection, Units (SD)	183U (78U)	185U (79U)

\* 21 children per group.

Table V: Subgroup analyses: Ankle dorsiflexion

Subgroup Analyses Passive Dorsiflexion		Baseline		26 months		Change		Mean difference between groups at 26mths	95% CI	<i>p</i>
		Mean	SD	Mean	SD	Mean	SD			
Both injection frequencies	Hemiplegia	8.1°	15.0°	0.5°	9.4°	-8.5°	14.0°	9.4°	2.6°, 16.2°	<b>0.01</b>
	Diplegia	7.7°	8.7°	9.9°	12.2°	+1.6°	12.0°			
	Difference: mean, 95% CI					10.1°	3.1°, 17.2°			
Hemiplegia	12-monthly	8.8°	17.5°	1.0°	11.5°	-8.1°	16.3°	-1.0°	-10.1°, 8.1°	0.82
	4-monthly	7.3°	12.5°	0.0°	7.0°	-9.0°	11.9°			
	Difference: mean, 95% CI					-0.9°	-14.8°, 13.0°			
Diplegia	12-monthly	6.6°	9.7°	7.5°	15.3°	+0.1°	12.2°	5.0°	-5.9°, 15.8°	0.39
	4-monthly	8.7°	8.0°	12.4°	7.4°	+3.1°	11.5°			
	Difference: mean, 95% CI					2.9°	--4.8°, 10.6°			

Negative (-) values for change scores indicate a loss of mean dorsiflexion range; positive (+) values indicate a gain in mean dorsiflexion range.



Figure 1: CONSORT diagram of the study

Figure 2: Mobility scales. A. Functional Mobility Scale, B. Functional Activity Questionnaire: Level, C. Functional Activity Questionnaire: Activities. Median change and interquartile range (IQR) scores for the 12-monthly (12m) and 4-monthly (4m) injection frequency groups are shown. Box depicts upper and lower quartiles with median subdividing the box, unless it falls on the quartile range. Whiskers span all data points within 1.5 IQR of the upper and lower quartiles. Dots represent outlying data points.