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Is There Any Benefit to Using Botulinum Toxin Type A in the Treatment of Lower Limb Spasticity in Younger Age Children with Cerebral Palsy?

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Abstract：This prospective comparative clinical trial examined the effectiveness of Botulinum toxin type A(BoNT-A)treatment for lower limb spasticity in younger age(< 3 years)children compared with older-age children(> 3 years)with cerebral palsy(CP)for improvements in spasticity, function, health-related quality of life(HRQOL), and parent perception of outcomes.

Method：Twenty-seven children with CP, ranging from 11 months to 8 years and 6 months, were grouped according to age and treatment- one younger age group treated with BoNT-A and physiotherapy($n=9$, mean age$=2^{+3}$ years SD= 4 months), a second younger age group treated with physiotherapy alone($n=9$, mean age= 2^{+8} years SD=7 months), and a third group of older aged children(> 3 years)treated with BoNT-A and physiotherapy($n=9$, mean age= 4^{+5} years, SD=15.1 months). Outcomes were evaluated for - spasticity using the Modified Tardieu Scale, activity limitation using the Gross Motor Function Measure(GMFM), a condition specific Pediatric Quality of Life Inventory™ and a parental questionnaire of perceived satisfaction with their child's performance. These measures were administered once prior to injection(baseline), then at one, three and six months post-injection.

Results：There was a significant reduction in spasticity for the younger age children treated with BoNT-A compared to controls retained at 6 month follow up. However, this was not accompanied by greater improvements in gross motor function. For the primary outcome there were

Key words：cerebral palsy, spasticity, botulinum toxin type A, pre-school infants, gross motor function, health-related quality of life, controlled clinical trial
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significant gains in gross motor function (GMFM-66) for the younger age treated children compared to older children at one month follow up (difference in means = 7.27, 95% CI 0.05,14.49, p = 0.019) and three months (difference in means = 7.86, 95% CI 1.04,14.68, p = 0.012) post-injection. A relationship between younger age BoNT-A treatment and improved parental perceptions was identified, attaining significance at three (p = 0.038) and six months (p = 0.029) post-injection.

Conclusions: This controlled trial suggests that there were additional benefits in treating younger age patients with intramuscular BoNT-A. Injections were safe, well tolerated and provided additional functional benefits and improvements in health related quality of life, when spasticity was treated in this younger age group compared to older children with CP.

Clinical Significance: Botulinum toxin A may provide a useful window of opportunity to enhance functional gains, improve HRQOL and achieve functional independence when provided at infant age.

Introduction

Botulinum toxin type A (BoNT-A) has gained wider appreciation as a focal treatment of spasticity in children with cerebral palsy (CP), since the early 1990's. There is good evidence that intramuscular injections of BoNT-A may inhibit the pre-synaptic release of acetylcholine, the neurotransmitter responsible for muscle contraction, resulting in a reduction in spasticity and it has been proposed that this may provide an opportunity to facilitate effective motor training. The duration of effectiveness of BoNT-A appears to be limited to three-to-six months though repeated injections are possible without serious adverse effects[4]. The question concerning the optimum age for the best efficacy for use of BoNT-A in children with CP remains unresolved.

It is thought that younger children will benefit more from BoNT-A combined with physiotherapy than older children and that this combined treatment may reduce or delay the need for surgery in ambulatory children. Treating children with CP with BoNT-A, at younger ages, reflects the hypothesis that as the child matures, the incidence of muscle shortening increases, reducing the dynamic component of spasticity. This may decrease the efficacy of BoNT-A as there is a direct correlation between the magnitude of response to treatment and the dynamic component of spasticity of the gastrosoleus[10].

This study was performed at the Children's Orthopaedic Centre in Mumbai, India, where children were treated with BoNT-A at younger ages (from 11 months) since 1999. Subjective findings suggested improvements in gross motor function along with a reduction in spasticity. However, benefits of treating children with CP at a younger age with BoNT-A have not yet been quantified.

Methods

This open-label study, combines data collected from a prospective six-month follow-up of children with CP (younger and older groups) and a matched group of retrospectively studied children from the medical chart review of younger age children with CP who did not receive BoNT-A for the treatment of lower limb spasticity.

Participants

The list of inclusion and exclusion criteria are summarised in Table 1a and 1b. Two sets of children were studied: -

Table 1a：- List of inclusion criteria.

Inclusion Criteria
・Diagnosis of CP with spastic motor type impairing the lower limbs, made by two clinical professionals(orthopaedic surgeon and physiotherapist).
・Attended physiotherapy for at least three months prior to the recommendation of BoNT-A injection.

Table 1b：- List of exclusion criteria.

Exclusion Criteria
・Presence of severe fixed contractures.
・Generalised athetosis and/or dystonia
・Previous BoNT-A injection(s)to the upper extremity, trunk or lower limb.
・Previous surgery.
・Very low cognition confirmed through clinical observation and anecdotal information from parents, as this would impact on the ability to co operate with physiotherapy.

Table 1c：- Patient groups.

Patient group	Description
Younger age	Prospectively studied children with CP, younger than 3 years of age, who received BoNT-A treatment for their spastic lower limb(s).
Older age	Prospectively studied children with CP, older than 3 years of age, who received BoNT-A treatment for their spastic lower limb(s).
Physiotherapy only	Retrospectively studied children with CP, younger than 3 years of age, who were recommended but did not receive BoNT-A treatment for their spastic lower limb(s).

(i)Prospective participants were younger than 10 years of age at the commencement of clinical treatment, which involved the use of BoNT-A. These children were then grouped into those younger than 3 years and those older than 3 years at first BoNT-A injection.

(ii)The retrospective group of children with CP were younger than 3 years of age when recommended for BoNT-A injection. However, their parents/caregivers decided not to opt for this treatment option and continued with physiotherapy alone.

Once informed consent was obtained, the medical records of the retrospective patients were accessed. The prospective patients completed a proforma and an appointment for baseline evaluation was made prior to the scheduled BoNT-A injection.

Study Protocol This study incorporated the domains specified in the International Classification of Functioning, Disability and Health[13], namely body structure(muscle impairment including spasticity), activity limitation(function) and Health-Related Quality of Life(HRQOL).

Prospectively studied children were evaluated at baseline(pre-injection), and post-injection at one, three and six month intervals. Evaluations were standardised and conducted by experienced physiotherapists with at least three years experience working in the field. Each evaluation consisted of measures of impairment of the lower limb and functional abilities. At six months, the parental perception of the child's functional status over the study period was evaluated using a parental questionnaire.

These children were separated into two groups based on their age when receiving the BoNT-A injection to those younger than 3 years and those older than 3 years of age. Medical records of the retrospective group of children with CP younger than 3 years of age were examined. Data were collected over two time periods- baseline and at six months, and included measures of impairment and functional abilities. All groups were matched along similar parameters The three groups are summarised in Table 1c.

Outcome Measures

At the level of body structure, the Modified

Tardieu Scale (MTS)[5] was used to assesses dynamic spasticity by measuring the catch range of motion (R1) at fast velocity (Tardieu V3)[5]. Acceptable inter-rater reliability[12] and validity[6] have been established.

At the level of activity limitation, the Gross Motor Function Measure-66 (GMFM-66), a Rasch analysed version specifically for children with CP, was used. The GMFM-66 contains selected items of the GMFM-88 to improve scalability[2] and is a valid and reliable measure of the achievement of motor activities[18]. Health Related Quality of Life was measured using the toddler and young child versions of the CP module of the Pediatric Quality of Life Inventory™ [20] (PedsQL™, Varni et al. 2006) The parent-proxy report of the toddler version of the PedsQL CP module was administered as a questionnaire that considers daily activities, movement and balance, pain and hurt, fatigue and eating activities. The infant version additionally considers school activities, and parent report of the child's communication skills. Varni et al[20]. reported strong reliability, validity and sensitivity of the PedsQL™ in CP.

A parental questionnaire was utilised to gather the parents' perception of change in their child's abilities following BoNT-A treatment. This was adapted from a questionnaire developed for a previous randomised controlled clinical trial by Wallen et al.[21], as there were no other relevant questionnaires that considered the functional movements and transitions of children with CP as young as 1 year of age.

Intervention

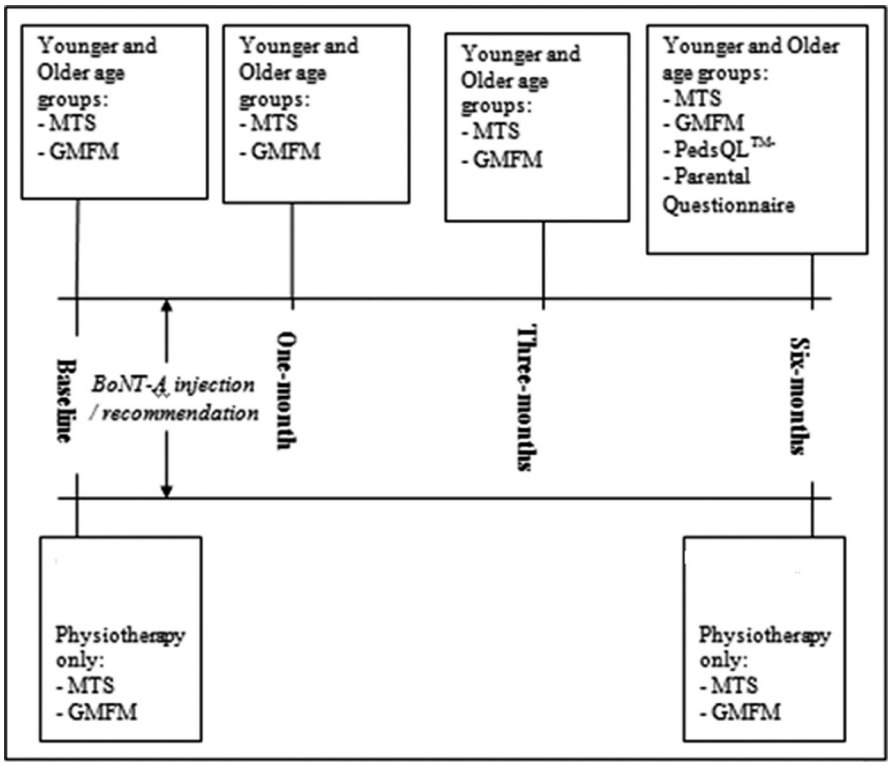
Intramuscular BoNT-A injections were administered, under mask anaesthesia, by a senior paediatric orthopaedic surgeon whose practice involves specifying BoNT-A doses at 1-3 U/kg of body weight of BOTOX® (Allergan, USA) for the gastro-soleus and 1-2 U/kg of body weight for other lower limb muscle groups. Correct needle placement was confirmed by observing needle motion during movement of the joint above or below the targeted muscle[9].

Both the retrospective and prospective groups continued with their physiotherapy regime, which was standardised based on good clinical practice. Each physiotherapy session consisted of passive stretching, followed by strength training and guided functional movements. Each child received at least one physiotherapy session per day for 30–45 minutes, 6 days per week, for 24 weeks duration post-injection/recommendation. The timing of outcome measures for the three sample groups is illustrated in Figure 1.

Analysis

The absolute amount of change was compared from baseline to each follow up interval in the total scores of the Tardieu R1, the GMFM-66, the PedsQL™ and parental questionnaire for the younger and older age groups. The absolute amount of change from baseline to follow up at six months was determined for the total R1 and GMFM-66 score for the physiotherapy alone group. The amount of change in spasticity (Tardieu R1), function (GMFM-66 score), HRQOL (PedsQL™) and parental questionnaire scaled scores was averaged within each sample group and compared between groups.

As samples were independent and of small sizes, nonparametric tests were used to conduct statistical analysis, using Data Analysis Plus in Microsoft Excel (XP edition). The Wilcoxon Rank Sum test was used to determine (a) any differences in impairment and function between the younger age and physiotherapy only groups, and (b) difference in the amount of change in impairment, and HRQOL between the treated



Key：-
MTS = Modified Tardieu scale(Boyd and Graham 1999)
BoNT-A = Botulinum toxin A injections
GMFM = Gross Motor Function Measure
PedsQL™= Pediatric Quality of Life Inventory(Cerebral Palsy module)
Fig. 1. Timing of outcome measures

younger and older age children. These comparisons were also used to test the hypothesis that younger age children with CP have greater changes in function compared to older children following treatment.

Confidence intervals for differences between two means were determined for the domains of impairment and function in younger age and physiotherapy only groups and the older age group, and HRQOL in younger and older age groups. Significance was set at a p-value of less than 0.05.

Results

Participant demographics

A total of 27 children with CP were entered into three patient groups(nine in each group). Participant demographics are included in Table 2. The dosages of BoNT-A per muscle group per limb and per child by sample group are summarised in Table 3.

The results of changes in Spasticity(R1), Gross Motor Function, Health Related Quality of life and parent reporting of changes in function between baseline and each follow up interval are summarised in Table 4.

Discussion

The primary results of this comparative study demonstrated a reduction in spasticity in the BoNT-A group when combined with physiotherapy, compared to physiotherapy alone. At six

Table 2：- Participant demographics

	Younger age group	Older age group	Physiotherapy only
Sample size	*n* = 9	*n* = 9	*n* = 9
Male/Female Ratio	M = 5 F = 4	M = 5 F = 4	M = 5 F = 4
Mean age (years)	2^{+3} SD = $0^{+4.23}$ (range 1^{+8} to 2^{+9})	4^{+6} SD = 1^{+3} (range 3^{+6} to 7^{+6})	2^{+1} SD = $0^{+7.33}$ (range 0^{+11} to 2^{+9})
Distribution of spastic motor type	7：diplegia 2：hemiplegia	8：diplegia 1：quadriplegia	6：diplegia 2：quadriplegia 1：hemiplegia
Mean baseline R2 of hamstrings (degrees of extension, Popliteal angle)	152.5 SD = 30.11 (range 90 to 180)	124.38 SD = 31.30 (range 85 to 180)	142.94 SD = 33.54 (range 90 to 180)
Mean baseline R2 of gastro-soleus (degrees of dorsiflexion, knee extended)	8.25 SD = 6.34 (range 0 to 15)	6.07 SD = 5.61 (range -5 to 15)	9.80 SD = 5.40 (range 0 to 15)
Number of children with CP who received concomitant casting in addition to BoNT-A treatment	9	9	N/A
Limbs casted	Right only：1 Left only：1 Bilateral：7	Right only：2 Left only：0 Bilateral：7	N/A
Mean duration of casting (weeks)	2^{+1} SD = 2.71 (range 1^{+5} to 2^{+6})	2 SD = 2.60 (range 1^{+4} to 2^{+4})	N/A
Mean hours of physiotherapy received per week	7.5 SD = 3.18 (range 4.5 to 13.5)	7.0 SD = 3.27 (range 4.5 to 13.5)	7.5 SD = 3.18 (range 4.5 to 13.5)
Number of children with CP taking anti-spasticity medication	5	5	5
Muscle groups targeted with spasticity treatment	16：Gastro-soleus 12：Hamstrings 3：Gracilis 7：Adductors 1：Rectus Femoris	14：Gastro-soleus 16：Hamstrings 6：Gracilis	12：Gastro-soleus 15：Hamstrings 5：Gracilis 2：Adductors
Number of children in each GMFCS level	Level I：3 Level II：4 Level III：1 Level IV：1 Level V：0	Level I：2 Level II：3 Level III：1 Level IV：2 Level V：1	Level I：2 Level II：0 Level III：2 Level IV：3 Level V：2

months, this effect was greater in the hamstrings, in the younger age group, compared to controls. At one month post-injection, the older children had a greater reduction in spasticity compared to younger treated children. However, this difference between groups was not sustained at three and six months.

In the gastro-soleus muscle, at six months, there was no greater reduction in spasticity for the younger age group treated with BoNT-A compared to physiotherapy alone. However, the reduction in spasticity in the physiotherapy only treated group is thought to have occurred gradually over six months, while the BoNT-A treat-

Table 3：- BoNT-A total dose and dosage ratio per muscle group per limb and per kilogram of body weight for each subject.

	Subject	Weight (kg)	Total dose administered (units)	Dosage ratio per muscle group (U/kg) per limb	Total dose per body weight (U/kg of bw)
Younger age group	1	10.0	60	3.0/ gastro-soleus	6
	2	10.0	100	2.0/ gastro-soleus 2.0/ hamstrings 1.0/ adductors	10
	3	8.0	100	3.0 gastro-soleus 2.0/ hamstrings	12.5
	4	10.0	100	3.0/ gastro-soleus 2.0/ hamstrings 1.0/ adductors	10
	5	7.0	100	3.0/ gastro-soleus 2.0/ hamstrings 1.0/ adductors 1.0/ gracilis	14.3
	6	10.0	130	3.0/ gastro-soleus 2.0/ hamstrings 1.0/ gracilis 1.0/ adductors 1.0/ rectus femoris	13.0
	7	12.0	60	3.0/ gastro-soleus 2.0/ hamstrings	5.0
	8	9.5	95	3.0/ gastro-soleus 2.0/ hamstrings	10.0
	9	10.0	30	3.0/ gastro-soleus	3.0
	Mean	*9.6* *SD = 1.4*	*86.1* *SD = 30.2*		*9.3* *SD = 3.9*
Older age group	1	10.0	100	2.0/ gastro-soleus 2.0/ hamstrings 1.0/ gracilis	10.0
	2	12.0	120	3.0/ gastro-soleus 2.0/ hamstrings	10.0
	3	20.0	140	1.5/ hamstrings 1.0/ gracilis 1.0/ adductors	7.0
	4	14.3	100	3.0/ gastro-soleus 2.0/ hamstrings	7.0
	5	10.0	100	3.0/ gastro-soleus 2.0/ hamstrings	10.0
	6	12.0	72	2.0/ hamstrings 1.0/ gracilis	6.0
	7	20.0	120	3.0/ gastro-soleus	6.0
	8	15.0	90	2.0/ hamstrings 1.0/ gastro-soleus	6.0
	9	10.0	100	3.0/ gastro-soleus 2.0/ hamstrings	10.0
	Mean	*13.7* *SD = 4.0*	*104.7* *SD = 19.7*		*8.0* *SD = 1.9*

Footnote：- **Mean dosage ratio per muscle group (U/kg) per limb**

	Younger age group	**Older age group**
Gastro-soleus	2.89, SD = 0.33	2.57, SD = 0.79
Hamstring	2.0, SD = 0.0	1.94, SD = 0.18

Table 4 : - Results of changes in Spasticity (R1), Gross Motor Function, Health Related Quality of life and parent report of changes in function between baseline and each follow up interval.

		Baseline-One month				Baseline-Three months			Baseline-Six months		
	Sample group	*n*	Mean change (SD)	Difference in means (95% CI)	*p*-value	Mean change (SD)	Difference in means (95% CI)	*p*-value	Mean change (SD)	Difference in means (95% CI)	*p*-value
R1 of Hamstrings	Older age	16	+ 36.88 (SD = 25.36)	19.38 (3.67,35.09)	$p = 0.046$	+ 28.13 (SD = 28.22)	0.21 (− 19.03,19.45)	$p = 0.82$	+ 24.38 (SD = 30.65)	1.04 (− 20.94,23.02)	$p = 0.78$
	Younger age	12	+ 17.5 (SD = 11.38)			+ 27.92 (SD = 17.9)			+ 25.42 (SD = 22.2)		
	Physiotherapy only	16							+ 5.94 (SD = 26.35)	19.48 (− 0.74,39.7)	$p = 0.037$
R1 of Gastrosoleus	Older age	13	+ 3.9 (SD = 5.25)	0.2 (− 3.58,3.98)	$p = 0.90$	+ 3.9 (SD = 5.25)	2.0 (− 2.55,6.55)	$p = 0.48$	+ 4.3 (SD = 5.14)	3.0 (− 1.99,7.99)	$p = 0.26$
	Younger age	16	+ 4.1 (SD = 4.17)			+ 1.9 (SD = 6.29)			+ 1.3 (SD = 7.42)		
	Physiotherapy only	16							− 2.0 (SD = 13.76)	3.3 (− 5.02,11.62)	$p = 0.37$
GMFM66	Older age	9	+ 5.28 (SD = 5.76)	7.27 (0.05,14.49)	$p = 0.019$	+ 4.24 (SD = 4.46)	7.86 (1.04,14.68)	$p = 0.012$	+ 9.29 (SD = 9.76)	7.1 (− 5.12,19.32)	$p = 0.10$
	Younger age	9	+ 12.55 (SD = 7.39)			+ 12.06 (SD = 7.65)			+ 16.39 (SD = 12.52)		
	Physiotherapy only	9							+ 8.65 (SD = 9.26)	7.74 (− 4.25,19.73)	$p = 0.086$
PedsQL™	Older age	9	+ 3.87 (SD = 8.63)	6.01 (− 7.42,19.44)	$p = 0.40$	+ 7.09 (SD = 7.67)	9.22 (− 4.99,23.43)	$p = 0.27$	9.68 (SD = 7.75)	11.00 (− 2.91,24.91)	$p = 0.10$
	Younger age	9	+ 9.88 (SD = 15.15)			+ 16.31 (SD = 16.78)			20.68 (SD = 16.32)		
	Physiotherapy only										
Parental Questionnaire	Older age	9	+ 8.95 (SD = 11.98)	3.79 (− 8.97,16.55)	$p = 0.35$	+ 10.25 (SD = 10.53)	4.78 (1.32,28.24)	$p = 0.038$	+ 8.59 (SD = 14.77)	23.38 (4.59,42.17)	$p = 0.024$
	Younger age	9	+ 12.74 (SD = 11.45)			+ 25.03 (SD = 13.96)			+ 31.97 (SD = 19.42)		
	Physiotherapy only										

Key:-
R1 = Catch range of motion at fast velocity
GMFM-66 = Gross Motor Function Measure (66-item)
PedsQLTM = Pediatric Quality of Life Disability Inventory (Cerebral Palsy module)

ed group experienced the greatest reduction in spasticity at one-month, and this effect declined by six months. When comparing the groups treated with BoNT-A at younger and older ages, it was determined that children injected after three years of age experienced a greater reduction in spasticity with the ankle joint becoming closer to neutral or in dorsiflexion range at one month, but this was not sustained at three and six months post-injection when it re-

turned to an equinus posture.

The results suggest that BoNT-A was useful, though its effect was limited in duration, in reducing dynamic spasticity. There were no differences in amount of reduction in spasticity according to age at initial injection. This partly supports the view that the effect on muscles is not limited by the patient's age[9)16)]. However, it does not provide strong evidence supporting this contention, as the age groups considered are younger than in those previous studies[16)14)].

The younger age group had greater improvements in gross motor function compared to older children at one and three months post-injection but this was not sustained at six months. Furthermore, there were no additional benefits for gross motor function, at six months, for the younger group compared to the physiotherapy alone group. These findings confirm the results of another study in children with CP where single or two level injections did not result in functional gains at six months compared to therapy alone[17)]. However, in this study, there is a new finding related to the enhanced outcome for younger age children with BoNT-A at one and three months. The reduction in spasticity enabled opportunities for enhanced motor outcomes when combined with a comprehensive physiotherapy program.

Systematic reviews[1)7)]and meta-analyses investigating gross motor function outcomes in response to BoNT-A with or without physiotherapy have conflicting findings with some reporting improved outcomes[15)11)]while others report no difference.[17)1)]Some studies suggest the GMFM-88 may not be sensitive to changes due to BoNT-A treatment as the effect of BoNT-A may be more on quality of movement or alignment of the task compared to attainment of the task[8)]. This current study overcame some of these issues by using the GMFM-66.

There were no differences between groups for improvements in the HRQOL according to the age of first injection. Varni et al.[20)]suggested that disease-specific symptoms tested in the CP module of the PedsQL™ may be indicators of HRQOL. They reported a significant correlation between difficulties in gross motor function and lower HRQOL. However, in the present study, the younger age group had significantly greater improvements in gross motor function when compared to the older age group but did not demonstrate respective gains in HRQOL using the PedsQL–CP module. To date there are no studies that have reported changes in HRQOL due to BoNT-A nor reports of condition specific measures of HRQOL that have measured changes in HRQOL due to spasticity management.

In contrast to the HRQOL outcomes, parents reported there were greater improvements in their perception of their child's transitional movements, for the younger age group compared to the older age children. These results, however, may be biased by the lack of blinding of the parents to their child's treatment.

It is important to acknowledge the influence of parental expectations prior to commencing treatment when reporting the results of parent perceptions, in regard to clinical treatment. Setting realistic goals with parents prior to treatment, may be important, in order to ascertain their level of expectations and inform them of the potential effects that might be achieved. In doing this, more accurate data related through proxy reports, may be collected.

Quantification of severity and the distribution of lower limb spasticity in children with cerebral palsy who were younger than three years of age presented some methodological challeng-

es. The inclusion criteria, as far as possible, addressed certain confounds, by having two independent confirmations of the diagnosis of CP and the dosage and theoretical construct of the physiotherapy was standardised. However, there were limitations.

The exclusion criteria sought to ensure that initial BoNT-A treatment of spasticity was the main focus of the study by excluding other movement disorders(using Sanger's definitions[19]), severe fixed contractures and previous BoNT-A injections. Importantly, some children with CP, included in this study, demonstrated some mild localised dystonia and mild to moderate fixed muscle contractures but dynamic spasticity appeared to be the main contributor to their clinical presentation.

Children in the present study received a substantial duration and intensity of physiotherapy, as compared with many western programmes. Participants had no major cognitive difficulties as these would impact on compliance with physiotherapy management, potentially confounding the impact of BoNT-A on the development of gross motor function.

The brevity of the recruitment time period meant that the number of eligible children was restricted and this small sample though matched on some key variables(age, gender) may lack statistical power. There may be a limitation in the potential reliability of some outcomes measures(spasticity and gross motor function)in younger age children due to compliance.

In the MTS, absolute changes in R1 were considered instead of proportional change, the difference between R1 and the muscle length at slow velocity(R2). Blair et al.[3]stated that the proportional change reflects the degree to which a pre-determined goal range of motion is achieved rather than how much change in spasticity had actually occurred. The approach adopted in the current study focussed on change from a stable baseline. Inter-rater variability was minimised by having the child assessed by the same physiotherapist.

Conclusion

There are benefits to using BoNT-A in younger age children with CP to reduce spasticity and improve gross motor function. Intramuscular BoNT-A injections combined with a standardised, intensive physiotherapy regime greatly improves gross motor function at one and three months follow up compared to similar treatment in older aged children. It also reduces hamstring spasticity at six months compared to physiotherapy alone.

In this prospective study, the groups of older and younger children with CP were matched for key demographics and interventions were carefully controlled for intensity and duration between groups. This study provides some new data with promising findings that needs to be replicated in a larger clinical trial.

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