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ORIGINAL ARTICLE

Does botulinum neurotoxin A make walking easier in children with cerebral palsy? A randomized clinical trial

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Abstract

Aim: To assess the effect of single botulinum neurotoxin A (BoNT-A) injections into the calf muscles on the gross energy cost of walking in children with cerebral palsy (CP) and to evaluate the effect of BoNT-A on walking capacity, physical activity, perceived changes in mobility, and pain.

Method: This was an industry-independent, randomized, quadruple-blind, placebo-controlled, multicentre trial (ClinicalTrials.gov registration: NCT02546999). Sixty-one children (33 male, median age [range] = 8 years [4–16 years]) with spastic CP and classified in Gross Motor Function Classification System (GMFCS) levels I and II allocated to single injections of either BoNT-A or 0.9% saline into the calf muscles. The main outcome was gross energy cost (J/kg/m); secondary outcomes were walking capacity, habitual physical activity, perceived change in mobility tasks, and calf pain at baseline, 4 weeks (P1), 12 weeks (P2), and 24 weeks (P3) after the injection.

Results: The mean change in energy cost did not differ significantly between groups at the primary time point P2 (−0.27 J/kg/m, 95% confidence interval − 0.91 to 0.36, $p = 0.404$), nor at P1 or P3. Regarding the secondary outcomes, there was some evidence of a larger reduction in pain intensity in the group given BoNT-A ($p = 0.043$).

Interpretation: One treatment with BoNT-A was not superior to placebo in making walking easier in children with CP classified in GMFCS levels I and II, at least in the short term. BoNT-A may have a pain-reducing effect.

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Abbreviations: CHQ, Child Health Questionnaire; COPM, Canadian Occupational Performance Measure; LMM, linear mixed model.

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Approximately 70% of children with cerebral palsy (CP) can walk independently[1] but have varying degrees of walking difficulties, such as impaired balance[2] and increased energy cost during walking,[3] compared to their typically developing peers. Moreover, fatigue[4] and pain[5] are often reported. This often leads to limited physical activity and participation in social activities.[6]

Spasticity is the dominant motor feature in CP and it is present in more than 80% of children.[7] A significant breakthrough in the treatment of spasticity was the introduction of intramuscular injections of botulinum neurotoxin A (BoNT-A) in the 1990s. In Norway, more than 50% of children with CP are currently treated with BoNT-A injections.[8] Among independent walkers, the calf muscles are most commonly treated with BoNT-A,[7] with the primary aim to correct spastic equinus gait. Despite the evidence that BoNT-A reduces spasticity being well documented, and that BoNT-A may improve equinus gait, the evidence for its effect on walking and performance is still limited and inconclusive.[9]

Recent concerns have suggested that BoNT-A injections might cause loss of contractile muscle elements and cause increased fibrosis, which might outweigh the positive short-term reduction in spasticity.[10,11] Chemodenervation after BoNT-A injection results in acute muscle atrophy and partial replacement of contractile muscle elements by fat and connective tissue.[10] Indeed, experimental studies in animals and humans suggested incomplete recovery of muscle morphology and function up to 6 to 12 months after injection. However, the changes in muscle morphology in animal models might not accurately mimic the changes observed in the spastic muscles of humans.[12] Furthermore, research into muscle volume alterations in children with CP suggested that BoNT-A injection may not have as profound an effect in humans as previously reported in animal models.[11,13] However, the long-term effects of BoNT-A on muscle morphology and properties remain understudied; further studies on the effect and possible detrimental consequences of treatment are needed.

The main objective of this trial was to investigate whether one treatment with BoNT-A into the calf muscles would make walking easier in children and adolescents with CP during the following 6 months. The primary outcome was gross energy cost. Secondary outcomes were walking capacity, daily activity, perceived performance, satisfaction related to mobility tasks, and calf pain. We hypothesized that injecting BoNT-A into the calf muscles would reduce energy cost during walking, improve walking capacity, increase habitual physical activity, improve perceived performance and satisfaction related to mobility tasks, and reduce pain.

What this paper adds

- A single botulinum neurotoxin A (BoNT-A) treatment into the calf muscles did not reduce the energy cost compared to placebo.
- There is a possible long-term reduction in energy cost after BoNT-A treatment into the calf muscles.
- BoNT-A treatment into the calf muscles may reduce calf pain in ambulatory children.
- No serious adverse events related to BoNT-A treatment were recorded.

METHOD

Study design

In this industry-independent, placebo-controlled superiority trial, participants were randomized to receive either an injection of BoNT-A or saline (placebo) into the calf muscles. The study was quadruple-blinded; the participants (and parents or carers), the physician injecting the solutions, the therapists assessing the possible effects, and the statistician were all blinded regarding allocation to BoNT-A or placebo. The allocation ratio was 1:1. Stratification was made according to centre and age group (4–10 years and 11–17 years 6 months) because supportive therapy varied between centres and because of the wide age range of participants. Randomization was performed using pre-randomized lists at each site using a web-based randomization system at the Unit of Applied Clinical Research, Norwegian University of Science and Technology. Assessments were made at baseline and 4 weeks (P1), 12 weeks (P2), and 24 weeks (P3) after the injection.

The trial was approved by the institutional ethics committees (Appendix S1) and conducted according to the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use good clinical practice. Monitoring was carried out according to a predefined plan, independently of the sponsor, and with no competing interests. Protocol modifications were reviewed by the approving ethics committees in all three countries; substantial modifications were reviewed by the Medicines Agency in all three participating countries. The processing of personal data was done according to procedures approved by the data protection official at each study centre. The study protocol has been published;[14] the latest protocol version is provided in Appendix S2. Two related papers, based on a subset of baseline data and thus not addressing the effect of BoNT-A, have also been published.[15,16]

Participants

Children and adolescents aged between 4 years and 17 years 6 months at the time of study inclusion, with spastic unilateral or bilateral CP, and where the responsible physician decided that single injections with BoNT-A into the calf muscles were indicated, were deemed eligible to participate. Further inclusion criteria were: (1) Gross Motor Function Classification System (GMFCS) levels I or II; (2) no treatment with BoNT-A into the lower limbs during the past 6 months;

(3) no orthopaedic surgery in the lower limbs during the last 2 years; and (4) the ability to understand verbal instructions.[17] The exclusion criteria are listed in Appendix S2. The study was conducted within a clinical setting between 2015 and 2021, involving five sites in Norway, one in Poland, and one in France.

Interventions

After providing written informed consent to participate in the study and agreeing to the publication of the results (participants or their caregivers), participants were randomized to single injections of either BoNT-A or 0.9% saline into the calf muscles. The appropriate identical-looking solutions of BoNT-A and saline were prepared at the pharmacies of each hospital and delivered in identical syringes to the doctors performing the injections.

The dosage of BoNT-A (either Botox or Allergan) used in this study was based on two international expert consensus papers[18,19] and clinical experience. The total maximum dose of BoNT-A per individual was 420 units. The maximum injected volume per injection site was 0.5 mL of a solution of 100 units of BoNT-A in 1 mL of 0.9% saline, or 0.5 mL of 0.9% saline only (placebo). Injections were given into both heads of the gastrocnemius muscle, and in the soleus muscle when indicated. No other muscles in the lower extremities were injected during the study period. The dose into the gastrocnemius muscle was 6 U/kg for unilateral treatment and 5 U/kg for bilateral treatment. The dose in the soleus muscle was 2 U/kg. Dosing tables are included in the study protocol shown in Appendix S2. The ultrasound-guided injections were administered under local anaesthesia; if desired, conscious sedation with oral or nasal benzodiazepines was offered in accordance with local guidelines.

Primary outcome

The primary outcome measure was gross energy cost during walking, obtained from a 5-Minute Walk Test performed along a 45-m pathway at a self-chosen comfortable speed.[20] Simultaneous measurements of the rate of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were performed using METAMAX, vII or vIIIb (CORTEX Biophysik, Leipzig, Germany), carried on the back with a facemask placed over the child's mouth and nose. Energy cost was estimated according to the following formula:

Energy cost (J/kg/m) = (4.960 × respiratory exchange ratio + 16.040) × VO_2 (ml/kg/min)/walking speed (m/min). Where VO_2 and VCO_2 are the average oxygen uptake and carbon dioxide production over a 1-minute steady state period during the last 2 minutes of the walking test respectively, relative to body weight (ml/kg/min). The respiratory exchange ratio was calculated by dividing VO_2 by VCO_2.

Secondary outcomes

Walking capacity was measured according to (1) the distance walked during a 1-Minute Walk Test,[21] where the participant was instructed to walk as fast as possible without running, and (2) the perceived exertion assessed using the OMNI Rating of Perceived Exertion scale scored after the 1-Minute Walk Test. The OMNI Rating of Perceived Exertion is a 10-point scale (0–10) validated in children with CP.[22]

Habitual physical activity was measured using two body-worn accelerometers (Axivity, Newcastle upon Tyne, UK) over 7 consecutive days after all four visits. Five weekdays of activity monitoring were selected for analysis. The time spent lying, sitting, standing, and walking during 3-second intervals was determined; the average total number of hours spent engaged in those activities during 24 hours (a full day–night cycle in a weekday) was reported. Sitting and lying were defined as sedentary behaviours, while standing and walking were defined as activity.

The Canadian Occupational Performance Measure (COPM)[23] was used to measure perceived change in performance and satisfaction with gross motor tasks. The instrument was administered as a semistructured interview focusing on relevant gross motor activities throughout the day. At baseline, the child was allowed to identify and prioritize up to three problem areas. The performance and satisfaction related to each problem were scored on a 10-point ordinal scale (1–10), where a higher score reflected greater performance and satisfaction respectively. Rescoring was done after all three visits. The average COPM scores for performance and satisfaction were each divided by the number of problem areas identified, giving two total average scores.

Pain was assessed by recording the intensity and frequency of calf pain as well as calf pain interfering with walking during the last 2 weeks. Parents were asked to record all pain sites on the body outline from the Brief Pain Inventory.[24] If calf pain was recorded, parents were asked to respond to the two questions on pain (i.e. 'how much' and 'how often') from the Child Health Questionnaire (CHQ), Norwegian version.[25] The item 'interference with walking' from the Brief Pain Inventory was used to capture the level of calf pain interfering with walking on a 0 to 10 numeric rating scale where 0 represents no interference and 10 is complete interference. Recordings were made for the right and left calves separately. A CHQ pain score that combined pain intensity and frequency according to the CHQ manual was provided for each calf.

The following background variables were recorded: (1) spasticity in the calf muscles assessed in the supine position using the Tardieu Scale scoring from 0 to 4;[26] and (2) passive ankle dorsiflexion with straight knee, measured using a manual goniometer (for the procedures, see Appendix S3).

Sample size

The sample size calculations were performed using a two-sample, two-sided Student's *t*-test to compare the change between groups in the primary outcome measure, energy cost, from baseline to P2. The estimate was based on a mean difference in change of 0.684 J/kg/m;[20] this value corresponds to a 10% change from a mean energy cost of 6.84 J/kg/m, as reported for a similar population with CP.[20] The specified change was slightly larger than the estimated smallest detectable difference in change in energy cost, reported to be 0.464 J/kg/m (or 6.8%).[20] Based on this and on the study by Schwartz et al.,[27] we defined a 10% improvement in the intervention group compared to placebo (i.e. 0.684 J/kg/m) to be clinically significant. The SD of change was set to one based on other intervention studies.[20,28] For a power of 80%, to detect a clinically significant difference in change in the primary outcome measure using a 5% significance level, a total sample size of 68 participants was needed. Accounting for a 30% dropout rate, we aimed for a total of 96 participants.

Statistical analyses

Data analysis was carried out according to the statistical analysis plan shown in Appendix S4 before unmasking group allocation. The primary analyses were carried out based on the intention-to-treat principle, using the full data set. For the primary outcome variable (energy cost), a linear mixed model (LMM) was used to analyse the difference in change between the treatment and the placebo groups from baseline to P1, P2, and P3, with P2 as the primary time point. The LMM included the main effects of time (baseline, P1, P2, and P3) and group (BoNT-A or placebo) and their interaction, while constraining the baseline means to be equal in the two groups because of the randomized design. There was some evidence of a centre effect for the primary outcome variable when introducing a fixed effect for 'hospital'. However, some centres had few participants, and the results with and without the centre effect were similar for all outcome variables. Thus, the results from the models without a centre effect are presented.

In an LMM, all participants with at least one non-missing observation for the outcome variable across the repeated measurements were included in the analysis. Within-subject correlations were modelled using a random participant-specific intercept. The results are presented as the estimated mean differences with a 95% confidence interval (CI) and *p*-values. Similar LMMs were used for all secondary outcome variables, except for the pain outcomes, which were analysed using a Mann–Whitney *U* test.

The residuals from the LMMs were checked for a normal distribution using visual inspection of histograms, Q–Q plots, and an Anderson–Darling test for normality. When the assumption was not met, a log-transformation of the outcome variable or appropriate non-parametric tests were used. The results gave similar conclusions as for the LMMs on the original scale; thus, the results from the latter models are shown for ease of interpretation. A value of $p < 0.05$ was considered statistically significant. No formal adjustments for multiple testing were made. The statistical analyses for pain were based on the data for one leg for each child. For children with unilateral CP, the affected leg was selected. For children with bilateral CP, the calf with the most pain (highest CHQ pain score) at baseline was selected. If the left and right combined CHQ pain score was equal, the right leg was selected.

The statistical analyses were performed in R using the package lme4 for the LMMs[29] and in SPSS v29 (IBM Corp., Armonk, NY, USA).

RESULTS

Among 141 children assessed for eligibility, 61 were included and randomized, representing the full analysis data set in which intention-to-treat was performed. Three participants did not receive the allocated treatment and were lost to follow-up. Of these three, one did not tolerate the injection procedure due to pain, one was withdrawn from treatment by the responsible medical doctor, and one was excluded because of error in the inclusion or exclusion criteria. In addition, three participants were excluded because of major protocol deviations, leaving a total of 55 participants in the per-protocol analyses, that is, 30 in the BoNT-A group and 25 in the placebo group (Figure S1). The three participants excluded from the study did not adhere to the treatment procedure with regard to doses and injected muscles.

Five participants in both groups received injections only in the gastrocnemius muscle; the remaining participants were injected in both gastrocnemius and soleus muscles. One participant did not tolerate the pain during the treatment procedure and did not receive the allocated treatment. This was the only adverse advent observed in the study. The baseline characteristics of the participants and the baseline values of the outcomes for all participants included are shown in Tables 1 and 2 respectively. The number of participants at each of the seven sites were: 2, 5, 6, 7, 8, 16, and 17.

All analyses were repeated using the per-protocol sample. The results were like those from the intention-to-treat analyses; thus, only the intention-to-treat results are reported.

Primary outcome

The change in energy cost after the three visits is shown in Figure 1. There was no statistically significant difference between the groups regarding a change in energy cost from baseline to P2 (Table 3), nor at the other time points (P1 and P3). There was a within-group estimated mean decrease in energy cost in both groups from baseline to P3, with a mean

TABLE 1 Participant characteristics for the full analysis data set ($n = 61$).

	Placebo group		BoNT-A group	
	n	Mean (SD)/median (25th to 75th centile)	*n*	Mean (SD)/median (25th to 75th centile)
Age (years)	28	7 (2)/7 (5–9)	33	9 (3)/8 (5–11)
Weight (kg)	28	29.5 (9.9)/26 (23–35)	33	31.4 (14.6)/26 (22–39)
Height (cm)	28	129.8 (14.3)/129 (120–140)	33	132.9 (20.2)/128 (118–146)
Sex, *n* (%)				
Females	13 (46)		15 (45)	
Males	15 (54)		18 (55)	
GMFCS level, *n* (%)				
I	27 (96)		26 (79)	
II	1 (4)		7 (21)	
Distribution, *n* (%)				
Unilateral	21 (75)		26 (79)	
Bilateral	7 (25)		7 (21)	
Previous BoNT-A injection into the lower limbs, *n* (%)				
No	10 (36)		11 (33)	
Yes	18 (64)		22 (67)	
No. of treatments in lower limbs, median (25th to 75th centile)	$n = 14$	3 (3–5)	$n = 17$	5 (2–6)
Tardieu score 0/1/2/3/4	32[a]	7/6/18/1/0	39[a]	11/2/22/2/0
Passive ADF	32[a]		39[a]	
Green, *n* (%)	11 (34.4)		14 (35.9)	
Yellow, *n* (%)	6 (18.8)		11 (28.2)	
Red, *n* (%)	15 (46.9)		14 (35.9)	

[a]Number of legs in each category. 25th to 75th centile: lower (25th) and upper (75th) quartiles. Passive ankle dorsiflexion (ADF) with extended knee is presented according to the traffic light model used in NorCP and CPUP (https://cpup.se/). Green indicates a normal range (ADF ≥ 10°); yellow alerts that passive range of motion is less than normal (ADF = 0–9); red indicates a severe decrease in passive range of motion (ADF <0).

Abbreviations: BoNT-A, botulinum neurotoxin A; GMFCS, Gross Motor Function Classification System.

change of −0.63 J/kg/m (95% CI −1.07 to −0.20, $p = 0.005$) for BoNT-A and −0.31 J/kg/m (95% CI −0.93 to 0.31, $p = 0.327$) for placebo, which was statistically significant in the BoNT-A group ($p = 0.005$) but not in the placebo group ($p = 0.176$).

Change in secondary outcomes

No significant difference in change between the groups was found with regard to the secondary outcomes of walking capacity, activity, and perceived change in performance or satisfaction in gross motor tasks (Table 3). There were within-group gradual improvements in perceived change in performance and satisfaction throughout the study period in both the BoNT-A and placebo groups, with strong evidence for improvement from baseline to P2 and P3.

The group injected with BoNT-A had a significantly greater decrease in the intensity of calf pain at P2 compared to the placebo group ($p = 0.043$), but not in pain frequency ($p = 0.425$) and interference with walking ($p = 0.690$). The distribution of the change score for pain intensity in the two groups is shown in Figure 2.

DISCUSSION

BoNT-A injections in the calf muscles were not superior to placebo in making walking easier for children with CP, measured as a reduction in gross energy cost or improved walking capacity, habitual physical activity, and performance and satisfaction regarding gross motor tasks. However, there was some evidence that the intensity of calf pain decreased in the group injected with BoNT-A compared to the placebo group.

We hypothesized that injections with BoNT-A into the calf muscles would make walking easier, due to improved ankle joint functioning after reduction in spasticity. Only a few studies investigated the effect of BoNT-A on cardiorespiratory measures, with inconsistent results. One non-randomized study found decreased energy expenditure after BoNT-A injections,[30] while two double-blind, placebo-controlled trials showed no significant effect on metabolic measures,[31,32] which is consistent with our findings. However, differences in the methods used and the time points measured make it difficult to compare other studies with the current results. A reduction in energy cost is expected because of increasing age,[33] which might explain the

TABLE 2 Summary of baseline values for the primary and the secondary outcomes ($n = 61$).

	n	Total sample	*n*	BoNT-A group	*n*	Placebo group
Primary outcome						
Energy cost (J/kg/m)	58	5.71 (1.93)	31	5.46 (1.60)	27	5.99 (2.25)
Secondary outcomes						
1MWT (m)	60	93.17 (17.77)	32	93.13 (17.68)	28	93.21 (18.21)
OMNI-RPE (0–10)	58	5.91 (3.17)	31	5.81 (3.37)	27	6.04 (2.98)
Daily activity (hours)	51	7.55 (2.37)	29	7.73 (2.50)	22	7.30 (2.21)
COPM satisfaction (0–10)	61	5.48 (1.99)	33	5.33 (2.02)	28	5.65 (1.98)
COPM performance (0–10)	61	4.86 (1.72)	33	4.92 (1.83)	28	4.80 (1.60)
Calf pain, median (25th to 75th centile)						
Intensity (1–7)	53	2 (1–3)	26	2 (1–3)	27	1 (1–3)
Frequency (1–7)	53	2 (1–3)	26	2 (1–3)	27	1 (1–3)
Interference with walking (1–10)	55	1 (1–4)	27	1 (1–4)	28	1 (1–4)

Data are mean (SD) unless otherwise stated.

Abbreviations: 1MWT, 1-Minute Walk Test; BoNT-A, botulinum neurotoxin A; COPM, Canadian Occupational Performance Measure; OMNI-RPE, OMNI Rating of Perceived Exertion.

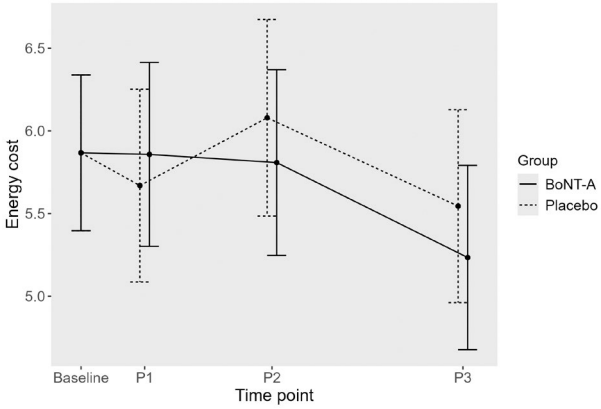

FIGURE 1 Change in energy cost from baseline to after each visit. Estimated mean values with 95% confidence intervals from the linear mixed model for energy cost (J/kg/m). P1, 4 weeks; P2, 12 weeks; P3, 24 weeks. Abbreviation: BoNT-A, botulinum neurotoxin A.

within-group decrease in both groups at P3. However, the reduction was about twice as large and significant in the BoNT-A group, suggesting a longer-term functional effect of the treatment, which was also suggested by Bjornson et al.[32]

We did not detect any difference in change between the groups with regard to the secondary outcomes. Children with CP often have reduced physical activity levels, falling short on the recommended levels for good health.[34] Accelerometry is a valid means to identify time spent sitting, lying, standing, and walking in children with CP.[35] However, factors like natural variability in behaviour require a larger sample size or more sensitive measures to detect the effect of treatment.

The COPM is a valid and reliable measure to detect changes in self-perceived activity performance and satisfaction.[36] Although not clinically relevant,[23] the within-group changes in the COPM improved significantly in both groups from baseline to P2 and P3; this could be a placebo response.

Because of the wide age range of the study participants (4–17 years 6 months), additional analyses, including age, age-by-group, and age-by-time interactions in the LMMs, were carried out using age defined according to two categories: 4 to 10 years and 11 to 17 years 6 months. No evidence of any interaction effects was found, but the power for the interaction analyses is probably low. The energy cost was significantly smaller and walking capacity was significantly larger among older children; however, the estimated group differences and change over time were not significantly influenced by adjusting for a main effect of age.

Pain is commonly reported in children with CP.[5] We found that 44% of participants experienced calf pain at baseline. The intensity of calf pain was reduced in the BoNT-A group at P2 compared to the placebo group, suggesting a possible pain-reducing effect of BoNT-A, as reported recently by Bonfert et al.[37] Their findings indicated that BoNT-A can provide clinically meaningful relief of spasticity-related pain in children and adolescents with CP, in addition to the spasticity-reducing effect. They also demonstrated that the pain-relieving effect was sustained with further improvement using successive BoNT-A injection cycles; however, the study lacked a control group and a placebo response should be considered when interpreting the effect. The mechanisms behind an observed pain-reducing effect are not clear, but a reduction in spasticity may be the result of blocking the nerve impulse relay and inhibiting the release of pain-inducing neurotransmitters.[38] Our results should be interpreted with caution because we did not adjust our analysis for multiple testing; in agreement with two recent reviews,[39,40] more research is needed.

Study strengths and limitations

The main strength of this study is its design including quadruple blinding. A further strength is that the study was carried out independently of the drug industry.

TABLE 3 Intention-to-treat analysis.

	P1 (4 weeks)			P2 (12 weeks)			P3 (24 weeks)		
	Estimate	95% CI	*p*	Estimate	95% CI	*p*	Estimate	95% CI	*p*
Primary outcome									
Energy cost (J/kg/m)	0.19	−0.43 to 0.81	0.550	−0.27	−0.91 to 0.36	0.404	−0.31	−0.93 to 0.31	0.327
BoNT-A	−0.01	−0.44 to 0.42	0.966	−0.06	−0.50 to 0.38	0.794	−0.63	−1.07 to −0.20	0.005
Placebo	−0.20	−0.66 to 0.27	0.404	0.21	−0.27 to 0.69	0.387	−0.32	−0.79 to 0.14	0.176
Secondary outcomes									
1MWT (m)	2.14	−3.69 to 7.98	0.471	−0.59	−6.47 to 5.30	0.845	−0.90	−6.70 to 4.89	0.760
BoNT-A	−0.66	−4.68 to 3.35	0.746	−2.02	−6.03 to 2.00	0.325	2.19	−1.85 to 6.23	0.289
Placebo	−2.81	−7.23 to 1.62	0.214	−1.43	−5.92 to 3.06	0.533	3.09	−1.26 to 7.45	0.164
OMNI-RPE (0–10)	0.04	−1.59 to 1.66	0.964	0.75	−0.91 to 2.41	0.376	0.06	−1.56 to 1.68	0.941
BoNT-A	−0.60	−1.81 to 0.62	0.335	−0.58	−1.80 to 0.63	0.347	−0.22	−1.43 to 0.99	0.718
Placebo	−0.64	−1.93 to 0.66	0.336	−1.33	−2.67 to 0.01	0.051	−0.28	−1.58 to 1.01	0.666
Daily activity (hours)	0.20	−0.93 to 1.33	0.731	0.26	−0.90 to 1.41	0.664	0.96	−0.18 to 2.10	0.100
BoNT-A	−0.12	−0.93 to 0.70	0.781	0.19	−0.61 to 0.98	0.643	0.06	−0.77 to 0.89	0.890
Placebo	−0.32	−1.21 to 0.58	0.492	−0.07	−1.02 to 0.88	0.888	−0.90	−1.81 to 0.00	0.051
COPM performance (0–10)	−0.47	−1.31 to 0.36	0.265	0.03	−0.82 to 0.88	0.943	0.70	−0.16 to 1.55	0.109
BoNT-A	0.44	−0.15 to 1.04	0.145	1.17	0.58 to 1.77	<0.001	1.90	1.29 to 2.52	<0.001
Placebo	0.92	0.27 to 1.56	0.005	1.14	0.48 to 1.81	0.001	1.21	0.55 to 1.86	<0.001
COPM satisfaction (0–10)	−0.08	−0.96 to 0.79	0.849	−0.27	−1.16 to 0.62	0.553	0.38	−0.52 to 1.27 to	0.409
BoNT-A	0.33	−0.29 to 0.95	0.304	0.85	0.23 to 1.47	0.007	1.62	0.98 to 2.25	<0.001
Placebo	0.41	−0.26 to 1.08	0.231	1.12	0.43 to 1.81	0.002	1.24	0.56 to 1.92	<0.001

Intention-to-treat analysis showing mean estimates with 95% CIs for between-group differences (BoNT-A and placebo) for P1 (4 weeks), P2 (12 weeks), and P3 (24 weeks) are shaded grey. Within-group changes (after the visits and at baseline) are presented in the unshaded rows. $p < 0.005$.

Abbreviations: 1MWT, 1-Minute Walk Test, walking as fast as possible; CI, confidence interval; COPM, Canadian Occupational Performance Measure; OMNI-RPE, OMNI Rating of Perceived Exertion.

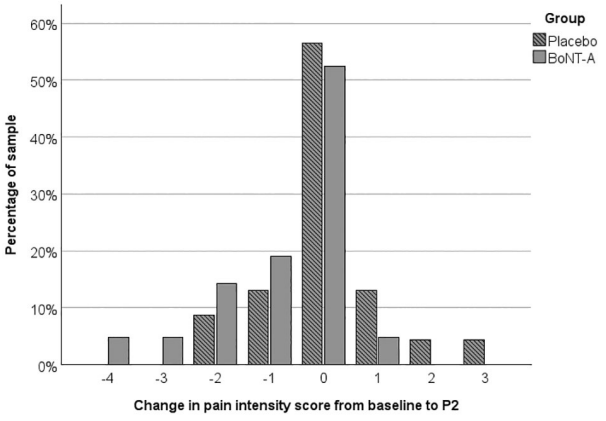

FIGURE 2 Change in calf pain intensity score from baseline to P2 (12 weeks) according to the percentage distribution of the sample. Negative values represent less pain, positive values represent increased pain, and 0 indicates no change from baseline to P2. Abbreviation: BoNT-A, botulinum neurotoxin A.

We were unable to reach the estimated sample size; thus, some caution is required regarding the interpretation of the results. Recruitment challenges were caused by the COVID-19 pandemic and fear of missing out on a well-established treatment. The latter was relevant whether or not participants were previously treated with BoNT-A. Even so, compared to other placebo-controlled and blinded studies on the effect of BoNT-A on walking, this study is strong in terms of the number of participants.[9]

The physician responsible for the regular CP follow-up and treatment had to find clinical evidence for the need of BoNT-A treatment into the calf muscles for participants to be deemed eligible. This can be considered a strength because it reflects real-life practice, but it also increases the diversity of participants. This could then be considered a limitation because it can introduce bias.

The randomization of participants was generally successful. However, the GMFCS levels were unevenly distributed

in the two groups; this may have influenced the estimated effect of BoNT-A. Furthermore, we recruited participants classified in GMFCS level I, making the results representative of these children.

The broad range of outcomes used, reflecting both capacity and performance, is a strength of the study. However, outcomes reflecting an individually perceived effect, like the Gait Outcomes Assessment List,[41] should be considered in future studies.

The participants in this study received only a single treatment with BoNT-A into the calf muscles; repeated BoNT-A injections may be necessary to measure an effect on walking. Younger children with CP have more dynamic contractures; therefore, they may respond better to BoNT-A injections.[12] The age range in the current study was quite wide, with a median age of 8 years; the wide age range may have made it more difficult to achieve a significant effect for the main outcome of energy cost. Moreover, the participants in this study included both children with no previous injections and children with previous injections, who were evenly distributed in both groups. Indeed, for the latter group, the median number of previous treatments in the BoNT-A group was five. It is assumed that the optimal treatment effect is obtained during the first 1 to 3 treatment sessions.[42] Lastly, one of the inclusion criteria in this study was no previous injections with BoNT-A during the last 6 months. In both groups, the time since the last treatment with BoNT-A was a median of 8 months. In light of previous results,[32] and in the current study, some participants may not have been 'clean' at the time of study inclusion, thus reducing the expected effect. Taken together, these aspects could, at least in part, contribute to the rejection of the main hypothesis.

Conclusion

Our study did not support the superiority of one treatment session with BoNT-A compared to placebo in making walking easier in children with CP classified in GMFCS levels I and II as reflected by reduced energy cost during comfortable walking. The estimated reduction in energy cost 24 weeks after the injection was greatest in the BoNT-A group; however, the difference from the placebo group was not statistically significant. This suggests a delay in functional response to BoNT-A. In addition, the results suggest that BoNT-A injected into the calf muscles may reduce pain in children with CP classified in GMFCS levels I and II, although this requires further research.

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

The following additional material may be found online:
Appendix S1: Registration data.
Appendix S2: The WE study protocol, version 7.
Appendix S3: Recordings and assessments.
Appendix S4: Statistical analysis plan.
Figure S1: Consolidated Standards of Reporting Trials flow diagram.

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