

Preoperative botulinum neurotoxin A for children with bilateral cerebral palsy undergoing major hip surgery: a randomized double-blind placebo-controlled trial

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ABBREVIATIONS

CPCHILD Caregiver Priorities and Child Health Index of Life with Disabilities
IQR Interquartile range
PPP Paediatric pain profile

AIM To assess whether preoperative botulinum neurotoxin A (BoNT-A) affects pain after major hip surgery for children with bilateral cerebral palsy (CP).

METHOD This was a randomized, parallel arms, placebo-controlled trial. Children with hypertonic CP aged 2 to 15 years awaiting bony hip surgery at a tertiary hospital were randomized to receive either BoNT-A or placebo injections into the muscles of the hip on a single occasion immediately before surgery. The primary outcome was the paediatric pain profile (PPP), which was assessed at baseline and weekly for 6 weeks. Treatment allocation was by minimization. Participants, clinicians, and outcome assessors were masked to group assignment.

RESULTS Twenty-seven participants (17 males, 10 females; mean 8y 8mo [SD 3y 9mo], range 3y 4mo–15y 10mo) were allocated to BoNT-A and 27 participants (14 males, 13 females; mean 8y 11mo [SD 3y 5mo], range 4y 1mo–15y 2mo) to placebo. Mean (SD) PPP at 6 weeks for the BoNT-A group ($n=24$ followed up) was 10.96 (7.22) and for the placebo group ($n=26$) was 10.04 (8.54) ($p=0.69$; 95% confidence interval [CI] $-4.82, 3.18$). There were 16 serious adverse events in total during 6 months of follow-up ($n=6$ in BoNT-A group).

INTERPRETATION Use of BoNT-A immediately before bony hip surgery for reducing postoperative pain for children with CP was not supported.

Cerebral palsy (CP) is the most common cause of physical disability in childhood. It affects up to three children per 1000 throughout Europe.¹ The Gross Motor Function Classification System (GMFCS) describes their level of motor ability and over 25 per cent of children with CP are in the most severely affected groups, classified as GMFCS levels IV and V. These children are not independently ambulant, are more likely to have cognitive and communication difficulties, and are at high risk of developing hip displacement, which causes pain for many children.^{2,3} Those children who present to orthopaedic services with progressive femoral head displacement require bony surgery (osteotomy) as long-term follow-up studies have demonstrated that this maintains the position of the femoral head in the acetabulum over time better than muscle surgery alone, and reduces the likelihood of a painful hip due to dislocation.^{4–7}

The management of pain in the severely neurologically impaired child undergoing hip surgery is challenging, and various strategies have been employed, including the use of postoperative epidurals.^{8,9} In a child with spasticity, abnormally high postoperative muscle tone may cause painful

muscle spasms.¹⁰ These involuntary and sustained muscle contractions are thought to contribute significantly to pain in children with CP. There are a number of treatments available for muscle spasm in CP; all are systemic except botulinum neurotoxin A (BoNT-A), which targets individual muscles by means of intramuscular injection. BoNT-A injection is a well-established and clinically effective treatment for muscle spasticity and the management of chronic pain in CP.^{11,12}

Research suggests it may have a beneficial effect in reducing postoperative pain due to spasticity.^{13–15} Barwood et al.¹³ reported that BoNT-A was effective in the postoperative period for children with CP undergoing muscle surgery only. However, describing pain in children with cognitive impairment is challenging.^{16–19} Hunt et al.¹⁹ provided a validated pain profile questionnaire, the paediatric pain profile (PPP), which measures pain in the more severely neurologically affected group of children with communication difficulties. Hunt et al. demonstrated that an observer's assessment of a child's pain into different levels of severity (none, mild, moderate, severe, or very severe) translated approximately into differences in scores

on the PPP of 10 points. The PPP provides a user-friendly pain score for this group of children, which was already in clinical use at the Evelina London Children's Hospital.

The aim of this study was to test the hypothesis that BoNT-A injections given to children with CP immediately before bony hip surgery affect pain experienced over a 6-week postoperative period.

METHOD

Study design

This was a single-centre, single surgeon, prospective, double-blind, parallel, superiority randomized placebo-controlled trial with an even randomization ratio, carried out at the Evelina London Children's Hospital, UK. Ethical approval was awarded by the National Health Service research ethics committee for Wales (11/WA/0010). The trial was overseen by a data monitoring committee.

Participants

The participants were recruited from children on the waiting list for hip surgery. Inclusion criteria included a diagnosis of bilateral hypertonic CP in GMFCS levels IV or V, aged 2 to 15 years inclusive, who required bony hip surgery for displacement, and whose communication ability was appropriate for the use of the PPP. Patients were excluded if they had received intramuscular BoNT-A within 4 months before surgery, had an acute and current systemic infection or illness, had a previous reaction to BoNT-A, were likely to receive at the time of drug administration medications that might interact with BoNT-A, or if their carers had insufficient understanding of English to complete the questionnaires. After screening, written information about the study including publication of results was given to the carers, and written consent for the trial was obtained at the pre-admission outpatient appointment held a few weeks before surgery.

Randomization and masking (blinding)

Participants were randomly allocated on the day of surgery to receive either BoNT-A or placebo (saline) injections in an even ratio. Treatment allocation was carried out independently of the research team, using a computerized minimization procedure by King's Clinical Trials Unit at King's College London. This was stratified by age (above or below 7y) and extent of surgery (unilateral or bilateral). An unmasked e-mail was then automatically generated and sent to the clinical trials pharmacist and to the Medicines for Children Research nurses. Two of these nurses drew up the trial drug into six 1mL syringes: either BoNT-A or placebo, both of which were clear colourless liquids. All syringes were labelled 'POPPIES trial drug'. The patient's carers and families and all other staff were blinded, including the trial coordinator who collected the data.

Procedures

The trial drug injections were given by the surgeon under ultrasound guidance into the adductor longus and magnus

What this paper adds

- Botulinum neurotoxin A (BoNT-A) does not reduce postoperative pain following bony hip surgery.
- BoNT-A also does not affect postoperative quality of life.

muscles, medial hamstrings, and iliopsoas muscles on both sides, after the patient was anaesthetized on the day of surgery. A dose of 12 units of Botox (Allergan Ltd., Marlow, UK) per kilogram body weight was chosen in accordance with the 2009 European Consensus statement for BoNT-A in children with CP.²⁰ The dilution was 50 units per millilitre of saline. All patients received a total of six injections (one site per muscle group). This meant that two units per kilogram could be used at each site, up to a total of 50 units at each site, and a total maximum of 300 units per child. There were no further BoNT-A or placebo injections during the trial.

Surgery for hip displacement was performed by one surgeon with assistants in accordance with established practice and surgical techniques.^{4,5} The indication for surgery was a migration index of more than 40 per cent. Even if normal, the contralateral hip was also treated for patients under the age of 10 years and for those with contralateral windsweep. All patients had a femoral osteotomy and release of adductor longus and iliopsoas tendons. If required, an open reduction was performed through an anterior approach. An acetabuloplasty was performed if there was residual on-table instability. No cast was applied. Postoperatively, epidural analgesia was continued until the morning of the second postoperative day. If the epidural was not successful, a morphine infusion was used. Discharge was planned for the fourth postoperative day.

Paediatric pain profile was recorded at the preoperative clinical appointment, within 24 hours of surgery, before discharge from hospital, at weekly intervals (for 5wks) by telephone, and in the clinic at 6 weeks after surgery. A parent/carer analogue scale of pain was collected at the same time as the PPP. Health-related quality of life, recorded using the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD), was measured at the outpatient clinic appointments preoperatively and at 6 weeks after surgery. A log of analgesic medication was collected daily while an inpatient, and at weekly intervals (for 5wks) by telephone, and in the clinic at 6 weeks after surgery. Other outcomes were recorded weekly by telephone for 5 weeks and then in the clinic at 6 weeks.

Clinical examination of ranges of movement, radiographic measurement of hip displacement using the Reimers' Migration Index^{21,22} and dysplasia using the Acetabular Index²³ were recorded at the baseline assessments, and at postoperative outpatient clinic appointments at 6 weeks, 3 months, and 6 months after surgery as part of the routine management of these children. PPP and CCHILD scores were also recorded at 3 months and 6 months postoperatively.

Outcomes

The primary outcome measure was the PPP.¹⁹ This questionnaire scores pain by rating 20 items of observed behaviour on an ordinal scale of 0 ('not at all') to 3 ('a great deal') with a composite score of 0 to 60. Six weeks after surgery was chosen as the primary end point on the basis of previous literature, which suggested a peak effect of BoNT-A approximately 3 weeks after injection, and our clinical experience of postoperative pain in this population.^{11,12} PPP was recorded at weekly time points to create a longitudinal measure of pain for each child and explore the optimal effects of BoNT-A throughout this postoperative phase.

The secondary outcomes included health-related quality of life using the CPCHILD questionnaire.²⁴ This assesses health status, comfort, well-being, and ease of caregiving of children with severe developmental disabilities, such as CP. The CPCHILD consists of 37 items categorized into six sections: activities of daily living, positioning, transferring and mobility, comfort and emotions, communication and social interaction, and health and overall quality of life. The caregiver rates each section based on the past 2 weeks. The maximum score is 100, and the higher the score the better the quality of life of the child. Other secondary outcomes included a parent/carer analogue scale of the child's pain in the previous 24 hours (0 being no pain to 10 being worst pain imaginable), length of stay in hospital, use of analgesic medication, time until return to school or daycare, the child's toleration of sitting in their usual chair, and the number of times the parents had to attend to their child during the night.

Adverse events and serious adverse events were assessed by the Chief Investigator with guidance from the King's Health Partners Clinical Trials Office, recorded and reported to the Data Monitoring Committee and the Medicines and Healthcare Products Regulatory Agency, UK.

Statistical analysis

It was considered that a reduction in the PPP score of 10 points would be clinically significant. This was the minimum clinically significant difference and assumed a more conservative effect than found previously.¹¹ This was also based on research that demonstrated that an observer's assessment of a child's pain into different levels of severity (none, mild, moderate, severe, or very severe) translated approximately into differences in PPP scores of 10 points.¹⁹ Power calculations were based on independent *t*-tests between two normally distributed groups. The computer program G*Power 3 (Universität Düsseldorf, Düsseldorf, Germany) was used to perform the calculations. It was assumed that the mean pain score in the control was 40 points on the PPP and that the mean score in the treatment group was 30 points. The standard deviation in both groups was assumed to be 12 points, equating to a standardized difference of 0.83. With these parameters, a standard significance level of 5 per cent and power of 80 per cent, the study required 24 patients in each group. The

aim was to recruit 56 patients, 28 for each trial arm, allowing for a potential 15 per cent loss to follow-up. The outcome was reported at multiple time points but the sample size calculation did not account for correlations between these measures.

All analyses followed the intention-to-treat principle (analysis groups defined by participants' random treatment allocation) and used Stata version 13 (StataCorp, College Station, TX, USA). A significance level of 5 per cent was used and all tests were two-sided. The primary outcome (PPP) and two secondary outcomes (CPCHILD and the parent/carer analogue pain scale) were analysed using linear mixed models. The dependent variable was outcome at the various post-randomization time points. The models' independent variables were the two randomization stratifiers (age category and extent of surgery), an indicator for time since randomization, treatment group, and an interaction between time and treatment group. In addition, the models included a random intercept for participant. The analysis models used maximum likelihood and assumed that the missingness mechanism was missing at random. For the primary end point (6wks after randomization), the estimated treatment was calculated using a linear combination of coefficients. A single summary score of analgesic use for each participant was calculated by summing together a daily frequency score for simple (range of 0–4/d) and opioid analgesics (range of 0–3/d). The opioids were given a weight of twice that of the simple analgesics. Five rounds of multiple imputation using chained equations (Stata command 'ice') were used to address missing analgesic data that were collected by telephone.²⁵ The effect of treatment on the summed scores was investigated using multiple regression where the independent variables were trial arm and the minimization stratifiers. Four outcomes that were not normally distributed (length of hospital stay, time to return to school or daycare, ability to tolerate sitting, and sleep disturbances) were analysed using the Mann–Whitney *U* test. The statistician remained blind until the end of the analyses.

RESULTS

Fifty-four participants were recruited from 21st September 2011 to 4th July 2014, 31 (57%) males and 23 (43%) females, mean age of 8y 10mo (SD 3y 7mo; range 3y 4mo–15y 10mo (Fig. S1, online supporting information). Fifty-four participants were randomized to either BoNT-A (*n*=27) or placebo (*n*=27). All of these were given the intervention and all but four (*n*=3 in BoNT-A group) were followed up at the primary end point (6wks after randomization). Summary statistics of the sample's demographic and clinical characteristics are presented in Table I. There was a substantial difference in GMFCS levels between the two treatment groups. Other demographic and clinical variables were well balanced, with the average number of comorbidities of 3.98 for the treatment group and 4.59 for the placebo group. Incontinence (25 treatment group, 21

placebo group) followed by epilepsy (17 treatment group, 16 placebo group) were the two most frequently reported comorbidities for both groups.

Summaries of PPP, CPCHILD, and the parent/carer analogue scale are provided in Table II; model-based estimated mean differences, *p*-values, and 95 per cent confidence intervals can be found in Table III. The group differences in PPP were small at all time points (Table II) and none, including at the primary end point, was found to be statistically significant (Table III). The estimated standardized group difference at 6 weeks after randomization was 0.11. The largest estimated difference was at 2 weeks after randomization and was in favour of intervention, but there was no trend across all time points.

There was no statistically significant difference between the treatment groups for CPCHILD. The standardized group difference was 0.28. The parent/carer analogue scale also showed no significant group differences. The largest group difference was at 2 weeks after randomization, but this was not consistent with the overall trend of a lack of effect.

There was slightly higher use of analgesics in the BoNT-A arm (mean 68.7, SD 24.0) compared to placebo (mean 63.9, SD 17.7). The estimated difference was not

Table I: Summaries of participants' demographic and clinical data at baseline

Variable	BoNT-A (<i>n</i> =27)	Placebo (<i>n</i> =27)
Age, y:mo, median (IQR)	8:3 (5:0–12:0)	8:1 (5:11–12:1)
Age categories, <i>n</i> (%)		
≤7y	13 (48)	13 (48)
>7y	14 (52)	14 (52)
Sex, <i>n</i> (%)		
Male	17 (63)	14 (52)
Female	10 (37)	13 (48)
Ethnicity, <i>n</i> (%)		
White	17 (63)	18 (67)
Asian	0 (0)	3 (11)
Black	7 (26)	4 (15)
Other	3 (11)	2 (7)
Extent of surgery, <i>n</i> (%)		
Unilateral	6 (22)	7 (26)
Bilateral	21 (78)	20 (74)
GMFCS level, <i>n</i> (%)		
IV	4 (15)	14 (52)
V	23 (85)	13 (48)
PPP, mean (SD)	12.81 (7.43)	12.52 (7.05)
CPCHILD, mean (SD)	50.74 (11.31)	53.39 (12.26)
Right migration %, median (IQR) ^a	61 (30–86)	35 (23–68)
Left migration, % (SD) ^b	46 (24–73)	44 (30.5–83.5)
Right acetabular index (SD) ^c	33 (26–40)	26.5 (19–33.5)
Left acetabular index (SD) ^c	32 (28–34)	32 (26.5–33)
Parent analogue scale, mean (SD)	2.84 (2.64)	2.46 (2.32)
Ability to tolerate sitting, minutes, median (IQR)	180 (120–300)	210 (90–300)
Sleep disturbances per night, median (IQR)	1 (0–3)	1 (0–3)

^a*n*=46. ^b*n*=47. ^c*n*=45. BoNT-A, botulinum neurotoxin A; IQR, interquartile range; GMFCS, Gross Motor Function Classification System; PPP, paediatric pain profile; CPCHILD, Caregiver Priorities and Child Health Index of Life with Disabilities.

Table II: Summaries of outcomes by treatment arm and time point

Outcome	1wk		2wks		3wks		4wks		5wks		6wks	
	BoNT-A	Placebo	BoNT-A	Placebo	BoNT-A	Placebo	BoNT-A	Placebo	BoNT-A	Placebo	BoNT-A	Placebo
PPP, mean (SD)	14.61 (8.55)	14.42 (8.34)	10.32 (6.47)	13.46 (9.36)	10.77 (8.24)	9.92 (7.26)	7.65 (5.23)	7.71 (6.29)	9.71 (7.23)	9.50 (8.66)	10.96 (7.22)	10.04 (8.54)
CPCHILD, mean (SD)	3.88 (2.56)	3.88 (2.69)	3.13 (2.38)	3.46 (2.04)	3.27 (2.64)	2.92 (2.08)	2.55 (1.61)	2.04 (1.99)	2.79 (2.15)	2.38 (2.37)	57.60 (12.95)	55.24 (12.93)
Parent analogue scale, mean (SD)											2.29 (2.10)	2.65 (2.33)

BoNT-A, botulinum neurotoxin A; PPP, paediatric pain profile; CPCHILD, Caregiver Priorities and Child Health Index of Life with Disabilities.

Outcome	1wk		2wks		3wks		4wks		5wks		6wks	
	EMD (95% CI)	p	EMD (95% CI)	p	EMD (95% CI)	p	EMD (95% CI)	p	EMD (95% CI)	p	EMD (95% CI)	p
PPP	0.46 (-3.57, 4.50)	0.82	-3.50 (-7.61, 0.62)	0.10	0.32 (-3.77, 4.41)	0.88	-0.07 (-4.25, 4.12)	0.98	0.09 (-3.96, 4.15)	0.97	0.82 (-3.18, 4.82)	0.69
CPCHILD											3.34 (-2.77, 9.45)	0.28
Parent analogue scale	0.31 (-0.95, 1.58)	0.63	-0.66 (-1.96, 0.64)	0.32	0.33 (-0.96, 1.62)	0.62	0.59 (-0.76, 1.93)	0.39	0.53 (-0.76, 1.81)	0.42	-0.19 (-1.46, 1.07)	0.77

EMD, estimated mean difference (botulinum neurotoxin A minus placebo); CI, confidence interval; PPP, paediatric pain profile; CPCHILD, Caregiver Priorities and Child Health Index of Life with Disabilities.

significant (mean difference of 5.02; 95% CI -6.71, 16.75, $p=0.39$). There was no difference in length of hospital stay (median 5d [interquartile range {IQR} 4–7] in BoNT-A arm and 5 days [IQR 5–6] in placebo arm; $z=-0.11$, $p=0.91$), in time until return to school/daycare (median 34d [IQR 22–49] in BoNT-A arm and 38d [IQR 28–43] in placebo arm; $z=0.50$), or ability to tolerate sitting at 6 weeks (median 240min [IQR 210–420] in BoNT-A arm and 300min [IQR 180–420] in placebo arm; $z=0.85$, $p=0.39$). There was no evidence of a treatment difference in number of sleep disturbances per night at 6 weeks (median 1 occasion [IQR 0–3] in BoNT-A arm and 1 occasion [IQR 0–3] in placebo arm; $z=-0.14$; $p=0.89$).

There were 16 serious adverse events in total during a 6-month follow-up period, with slightly fewer ($n=6$) in the BoNT-A trial arm. There was one death in the placebo arm ($n=1$). Other events were prolonged hospital stay ($n=5$), hospitalization ($n=8$), seizures ($n=1$), and pyrexia ($n=1$). There were 302 adverse events in total ($n=156$ in BoNT-A group). Of these, none were related to the trial drug, and 219 were unremarkable postoperative findings. There was no evidence of a relationship between trial arm and intensity of adverse events ($\chi^2=0.83$, $p=0.66$).

DISCUSSION

This was a randomized double-blind placebo-controlled trial to study the effect of preoperative BoNT-A on postoperative pain in children with CP. The trial demonstrated no difference when using a validated and widely used pain score (the PPP), and a robust methodology and statistical analysis. This result is supported by the secondary outcomes, that is, the CPCHILD quality of life index and a simple pain score out of 10. Therefore the evidence does not support the technique described here as an effective strategy for managing this difficult recovery period for these complex patients.

In their randomized placebo-controlled study of 16 children, Barwood et al.¹³ recorded a reduction in pain after adductor release surgery if 8 units per kg of BoNT-A was injected bilaterally into the adductor muscle area beforehand. This was a small trial with no formal blinding, and the postoperative pain was measured by the nurses and trial coordinator using a score out of 3 and the postoperative analgesia that was given. Nevertheless we found it compelling enough to conduct a larger trial after more major surgery. In their study, the muscles released at surgery had also been targeted by the trial drug, so we thought it clinically and methodologically sound to do the same.

In the Barwood et al.¹³ cohort, the BoNT-A was injected 5 to 10 days in advance of surgery, and the reduction in pain was recorded mainly during the first 48 hours, when painful spasms are normally at their worst. We considered injection of BoNT-A in advance because of its delayed onset, but ethically we could not justify it. In any case, if there was an effect, it should have been detected by the pain scores during the weeks that followed discharge,

as BoNT-A is known to have an effect over a number of months. We recorded a maximum but not statistically significant difference in pain scores between the groups after 2 weeks, and this could fit with the expected effect of the BoNT-A.

The surgery conducted for the Barwood et al. patients was considerably less extensive than for our patients, and they used double the dose of BoNT-A spread over two sites per muscle group. We acknowledge, therefore, that we might have had a positive result if we had used a larger dose and used more than one injection site, as these are relatively large muscles. On the other hand, our injections were arguably more accurate, as they were guided by ultrasound and performed under general anaesthetic.

Although the PPP is well validated, it may be argued that it is not sensitive enough to detect a difference between the two groups. It was intended for the measurement of chronic pain, rather than pain in the acute postoperative period. BoNT-A has been shown to be useful for pain management for the chronic pain of CP.¹¹ A difference in postoperative pain might be detectable using a pain score designed for this purpose.

Although we are anecdotally aware of the common use of BoNT-A for postoperative pain management after major hip surgery, we have been unable to demonstrate its benefit.

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Consolidated Standards of Reporting Trials (CONSORT) diagram of POPPIES trial.

REFERENCES

- Stanley F, Blair E, Alberman E. Cerebral Palsies: Epidemiology and Causal Pathways. London: Mac Keith Press, 2000.
- Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; **39**: 214–23.
- Valencia FG. Management of hip deformities in cerebral palsy. *Orthop Clin North Am* 2010; **41**: 549–59.
- Dhawale AA, Karatas AF, Holmes L, Rogers KJ, Dabney KW, Miller F. Long-term outcome of reconstruction of the hip in young children with cerebral palsy. *Bone Joint J* 2013; **95-B**: 259–65.
- Rutz E, Vavken P, Camathias C, Haase C, Jünemann S, Brunner R. Long-term results and outcome predictors in one-stage hip reconstruction in children with cerebral palsy. *J Bone Joint Surg Am* 2015; **97**: 500–6.
- Cornell MS, Hatrick NC, Boyd R, Baird G, Spencer JD. The hip in children with cerebral palsy. Predicting the outcome of soft tissue surgery. *Clin Orthop Relat Res* 1997; **340**: 165–71.
- Shore BJ, Yu X, Desai S, Selber P, Wolfe R, Graham HK. Adductor surgery to prevent hip displacement in children with cerebral palsy: the predictive role of the gross motor function classification system. *J Bone Joint Surg Am* 2012; **94**: 326–34.
- Nolan J, Chalkiadis GA, Low J, Olesch CA, Brown TC. Anaesthesia and pain management in cerebral palsy. *Anaesthesia* 2000; **55**: 32–41.
- Verrotti A, Greco R, Spalice A, Chiarelli F, Iannetti P. Pharmacotherapy of spasticity in children with cerebral palsy. *Pediatr Neurol* 2006; **34**: 1–6.
- Roscigno CI. Addressing spasticity-related pain in children with spastic cerebral palsy. *J Neurosci Nurs* 2002; **34**: 123–33.
- Lundy CT, Doherty GM, Fairhurst CB. Botulinum toxin type A injections can be an effective treatment for pain in children with hip spasms and cerebral palsy. *Dev Med Child Neurol* 2009; **51**: 705–10.
- Preiss RA, Condie DN, Rowley DI, Graham HK. The effects of botulinum toxin (BTX-A) on spasticity of the lower limb and on gait in cerebral palsy. *J Bone Joint Surg Br* 2003; **85**: 943–8.
- Barwood S, Baillieu C, Boyd R, et al. Analgesic effects of botulinum toxin A: a randomized, placebo-controlled clinical trial. *Dev Med Child Neurol* 2000; **42**: 116–21.
- Hamdy RC, Montpetit K, Raney EM, et al. Botulinum toxin type A injection in alleviating postoperative pain and improving quality of life in lower extremity limb lengthening and deformity correction: a pilot study. *J Paediatr Orthop* 2009; **29**: 427–34.
- Dohin B, Garin C, Vanhems P, Kohler R. Botulinum toxin for postoperative care after limb surgery in cerebral palsy children [In French]. *Rev Chir Orthop Reparatrice Appar Mot* 2007; **93**: 674–81.
- Houlihan CM, O'Donnell M, Conaway M, Stevenson RD. Bodily pain and health-related quality of life in children with cerebral palsy. *Dev Med Child Neurol* 2004; **46**: 305–10.
- Oberlander TF, O'Donnell ME. Beliefs about pain among professionals working with children with significant neurologic impairment. *Dev Med Child Neurol* 2001; **43**: 138–40.
- McKernan KA, Kieckhefer GM, Engel JM, Jensen MP, Labyak S. Pain in children with cerebral palsy: a review. *J Neurosci Nurs* 2004; **36**: 252–9.
- Hunt A, Goldman A, Seers K, et al. Clinical validation of the paediatric pain profile. *Dev Med Child Neurol* 2004; **46**: 9–18.
- Heinen F, Desloovere K, Schroeder AS, et al. The updated European Consensus 2009 on the use of botulinum toxin for children with cerebral palsy. *Eur J Paediatr Neurol* 2010; **14**: 45–66.
- Reimers J. The stability of the hip in children: a radiological study of the results of muscle surgery in cerebral palsy. *Acta Orthop Scand Suppl* 1980; **184**: 1–100.
- Scrutton D, Baird G. Surveillance measures of the hips of children with bilateral cerebral palsy. *Arch Dis Child* 1997; **76**: 381–4.
- Cooke PH, Cole WG, Carey RP. Dislocation of the hip in cerebral palsy. Natural history and predictability. *J Bone Joint Surg Br* 1989; **71**: 441–6.
- Narayanan UG, Fehlings D, Weir S, Knights S, Kiran S, Campbell K. Initial development and validation of the caregiver priorities and Child Health Index of Life with Disabilities (CPCCHILD). *Dev Med Child Neurol* 2006; **48**: 804–12.
- Royston P. Multiple imputation of missing values. *Stata J* 2004; **4**: 227–41.

RESUMEN

NEUROTÓXINA A BOTULÍNICA PREOPERATORIA PARA NIÑOS CON PARÁLISIS CEREBRAL BILATERAL QUE VAN A SER SOMETIDOS A UNA CIRUGÍA MAYOR DE CADERA: UN ENSAYO ALEATORIO, DOBLE CIEGO, CONTROLADO CON PLACEBO

OBJETIVO Evaluar si la neurotoxina A botulínica preoperatoria (BoNT-A) afecta el dolor después de una cirugía mayor de cadera en niños con parálisis cerebral bilateral (PC).

MÉTODO Este fue un ensayo aleatorio, con brazos paralelos, controlado con placebo. Los niños con PC hipertónica de 2 a 15 años de edad que esperaban una cirugía de cadera en un hospital terciario se escogieron al azar para recibir inyecciones de BoNT-A o de placebo en los músculos de la cadera una sola administración previa a la cirugía. El resultado primario fue el perfil de dolor pediátrico (PPP, siglas en inglés), que se evaluó al inicio del estudio y semanalmente durante 6 semanas. La asignación del tratamiento fue por minimización. Tanto los participantes, como los clínicos y evaluadores de resultados, eran desconocidos para la asignación de grupo.

RESULTADOS Veintisiete participantes (17 varones y 10 mujeres; medios 8 años 8 meses) [Desviación Estandar SD 3 años 9 meses], rango 3 años 4 meses-15 años 10 meses) se les administro BoNT-A y 27 participantes (14 varones y 13 mujeres; media 8 años 11 meses [SD 3 años 5 meses], rango 4 años 1 mes – 15 años 2 meses) a placebo. La PPP media (SD) a las 6 semanas para el grupo de BoNT-A ($n = 24$ seguidas) fue de 10,96 (7,22) y para el grupo de placebo ($n = 26$) fue de 10,04 (8,54) ($p = 0,69$; intervalo de confianza del 95% [CI, siglas en inglés] -4,82, 3,18). Hubo 16 eventos adversos graves en total durante 6 meses de seguimiento ($n = 6$ en el grupo BoNT-A).

INTERPRETACIÓN El uso de BoNT-A inmediatamente antes de la cirugía de cadera con el fin de reducir el dolor postoperatorio en niños con PC no fue consistente.

NEUROTOXINA BOTULÍNICA A PRÉ-OPERATÓRIA PARA CRIANÇAS COM PARALISIA CEREBRAL BILATERAL SUBMETIDAS A GRANDE CIRURGIA DE QUADRIL: UM ESTUDO RANDOMIZADO, DUPLO-CEGO, CONTROLADO POR PLACEBO

OBJETIVO Avaliar se a neurotoxina botulínica tipo A (BTA) pré-operatória A afeta a dor após grande cirurgia de quadril em crianças com paralisia cerebral bilateral (PC).

MÉTODO Este foi um estudo randomizado, com braços paralelos e controlado por placebo. Crianças com PC espástica com idade entre 2 a 15 anos aguardando cirurgia óssea de quadril em um hospital terciário foram randomizadas para receber ou BTA ou injeções de placebo nos músculos do quadril em uma única ocasião imediatamente antes da cirurgia. O desfecho primário foi o perfil de dor pediátrica (PDP), que foi avaliado na linha de base e semanalmente por 6 semanas. A alocação de tratamento foi por minimização. Os participantes, clínicos e avaliadores de resultados foram cegados quanto a atribuição de grupo.

RESULTADOS Vinte e sete participantes (17 homens, 10 mulheres; média de 8 anos e 8 meses [DP 3 anos e 9 meses], com idade entre 3 anos e 4 meses à 15 anos e 10 meses) foram alocados para o grupo BTA e 27 participantes (14 homens, 13 mulheres; média de 8 anos e 11 meses [DP 3 anos e 5 meses], com idade entre 4anos e 1mês à 15anos e 2 meses) foram alocados no grupo placebo. A média (DP) do PDP às 6 semanas para o grupo BTA ($n = 24$) foi de 10,96 (7,22) e para o grupo placebo ($n = 26$) foi de 10,04 (8,54) ($p = 0,69$; intervalo de confiança de 95% [IC] -4,82, 3,18). Houve 16 eventos adversos sérios no total durante 6 meses de acompanhamento ($n = 6$ no grupo BTA).

INTERPRETAÇÃO O uso da BTA imediatamente antes da cirurgia óssea do quadril para reduzir a dor pós-operatória em crianças com PC não foi apoiado.