A randomised double-blind placebo-controlled trial of pre-operative botulinum toxin A for children with bilateral cerebral palsy undergoing major hip surgery

Elspeth Will MSc, MCSP[1], Nicholas Magill MSc[2], Rebecca Arnold BSc[1], Megan Davies BSc[1], Gary Doherty MB[3], Charlie Fairhurst[1], Professor Andreas Roposch MD MSc FRCS[4], Claire Lundy MB[3], Fabian Norman-Taylor FRCS[1]

[1]Evelina London Children's Hospital; [2] Department of Biostatistics & King's Clinical Trials Unit, Institute of Psychiatry, Psychology & Neuroscience at King's College London; [3]Royal Belfast Hospital for Sick Children, [4]Institute of Child Health, University College London.

Corresponding author:
Mr Fabian Norman-Taylor, Department of Paediatric Orthopaedics, Evelina London Children's Hospital London SE1 7EH, UK; fabian.norman-taylor@gosh.nhs.uk

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Abstract

Aim

To assess whether pre-operative botulinum toxin A (BTX-A) affects pain following major hip surgery for children with cerebral palsy (CP).

Method

Randomised, parallel arms, placebo-contolled trial. Children with hypertonic CP aged 2-15 years awaiting bony hip surgery at a tertiary hospital were randomised to receive either BTX-A or placebo injections into the muscles of the hip on a single occasion immediately prior to surgery. The primary outcome was the Paediatric Pain Profile (PPP), which was assessed at baseline and weekly for six weeks. Treatment allocation was by minimisation. Participants, clinicians and outcome assessors were masked to group assignment.

Results

Twenty-seven participants (17 males; mean 8 years 8 months) were allocated to BTX-A and 27 (14 male; mean 8 years 11 months) to placebo. Mean (SD) PPP at six weeks for the BTX-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% CI -4.82, 3.18). There were 16 serious adverse events in total during six months of follow-up (n=6 in BTX-A group).

Interpretation

Use of BTX-A immediately before bony hip surgery for reducing post-operative pain for children with CP was not supported.

Trial registration

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Funding

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What this paper adds

- BTX-A does not reduce post-operative pain if used in this way.
- BTX-A also does not affect post-operative quality of life.

Cerebral palsy (CP) is the commonest 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% of children with CP are in the most severely affected groups, levels IV and V. These children are not independently ambulant and 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 post-operative epidurals.[8,9] In a child with spasticity abnormally high post-operative 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 cerebral palsy; all are systemic except botulinum toxin, which targets individual muscles by means of intramuscular injection. Botulinum toxin type A (BTX-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 post-operative pain due to spasticity.[13-15] Barwood et al reported that BTX-A was effective in the post-operative period for children with cerebral palsy undergoing muscle surgeryonly.[13]. However, describing pain in children with cognitive impairment is challenging.[16-19] Hunt et al. 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.[19] Hunt 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 ten points. The PPP provides for this group of children a user-friendly pain score, which was already in clinical use in our hospital.

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

Methods

Study Design

This was a single centre, single surgeon, prospective, double-blind, parallel, superiority randomised placebo-controlled trial (RCT) with an even randomisation ratio, carried out in a United Kingdom tertiary children's hospital. Ethical approval was awarded by the NES 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 with GMFCS levels IV or V, aged 2-15 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 BTX-A within 4 months prior to surgery, had an acute and current systemic infection or illness, had a previous reaction to BTX-A, were likely to receive at the time of drug administration medications that might interact with BTX-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 out-patient appointment held a few weeks prior to surgery.

Randomisation and masking (blinding)

Participants were randomly allocated on the day of surgery to receive either BTX-A or placebo (saline injections) in an even ratio. Treatment allocation was carried out, independently of the research team, using a computerised minimisation procedure by King's Clinical Trials Unit at King's College London. This was stratified by age (above or below 7 years) and extent of surgery (unilateral or bilateral). An unmasked email was then automatically generated and sent to the clinical trials pharmacist and to the Medicines for Children Research Nurses (MCRN). Two of these nurses drew up the trial drug into six 1ml syringes: either BTX-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 co-ordinator who collected the data.

Procedures

The trial drug injections were given by the surgeon under ultrasound guidance into the adductor longus and magnus muscles, medial hamstrings and iliopsoas muscles on both sides, after the patient was anaesthetised on the day of surgery. A dose of 12 units of Botox® (Allergan Ltd., Marlow, Buckinghamshire) per kilogram body weight was chosen in accordance with European Consensus statement 2009 for BTX-A in children with CP.[20] The dilution was 50 units per millilitre of saline. All patients received a total of 6 injections (one site per muscle group). This meant that 2 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 BTX-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%. 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. Post-operatively, epidural analgesia was continued until the morning of the second post-operative day. If the epidural was not successful, a morphine infusion was used. Discharge was planned for the fourth post-operative day.

PPP was recorded at the pre-operative clinical appointment, within 24 hours of surgery, before discharge from hospital, at weekly intervals (for 5 weeks) 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 qualify of life, recorded using the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD), was measured at the outpatient clinic appointments pre-operatively and at 6 weeks after surgery. A log of analgesic medication was collected daily while an inpatient and at weekly intervals (for 5 weeks) 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 (RMI)[21,22] and dysplasia using the Acetabular Index (AI)[23] were recorded at the baseline assessments, and at post-operative outpatient clinic appointments at 6 weeks, 3 months and 6 months after surgery as part of the routine management of these children. PPP and CPCHILD scores were also recorded at 3 and 6 months post-operatively.

Outcomes

The primary outcome measure was the PPP.[19] This questionnaire scores pain by rating twenty 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 botulinum toxin approximately 3 weeks post injection, and our clinical experience of post-operative 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 BTX-A throughout this post-operative phase.

The secondary outcomes included health-related quality of life using the CPCHILD questionnaire.[24] This assesses health status, comfort, wellbeing and ease of caregiving of children with severe developmental disabilities, such as CP. The CPCHILD consists of 37 items categorised into six sections: activities of daily living, positioning, transferring and mobility, comfort and emotions, communication and social interaction, health and overall quality of life. The caregiver rates each section based on the past two 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 day-care, the child's toleration of sitting in their usual chair and the number times the parents had to attend to their child during the night.

Adverse events and serious adverse events were assessed by the CI with guidance from the King's Health Partners Clinical Trials Office, recorded and reported to the Data

Monitoring Committee (DMC) and MHRA (Medicines and Healthcare Products Regulatory Agency, United Kingdom).

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 ten points.[19] Power calculations were based on independent t-tests between two normally distributed groups. The computer program 'G*Power 3' 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 standardised difference of 0.83. With these parameters, a standard significance level of 5% and power of 80%, 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% 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. A significance level of 5% 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-randomisation time points. The models' independent variables were the two randomisation stratifiers (age category and extent of surgery), an indicator for time since randomisation, 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 endpoint (six weeks after randomisation), 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/day) and opioid analgesics (range of 0-3/day).

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 minimisation stratifiers. Four outcomes that were not normally distributed (length of hospital stay, time to return to school or day-care, ability to tolerate sitting, and sleep disturbances) were analysed using the Mann-Whitney 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 (Figure 1). Fifty-four participants were randomised to either botulinum toxin (n=27) or placebo (n=27). All of these were given the intervention and all but four (n=3 in botulinum toxin group) were followed up at the primary end point (6 weeks after randomisation). Summary statistics of the sample's demographic and clinical characteristics are presented in Table 1. 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 co-morbidities 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 co-morbidities for both groups.

Table 1. Summaries of participants' demographic and clinical data at baseline

Variable		**Botulinum toxin (n=27)**	**Placebo (n=27)**
Age (median; IQR)		8.3 (5.0-12.0)	8.1 (5.9-12.1)
Age categories	≤7 years old	13 (48)	13 (48)
(n; %)	>7 years olds	14 (52)	14 (52)
Sex (n; %)	Male	17 (63)	14 (52)
	Female	10 (37)	13 (48)
Ethnicity (n; %)	White	17 (63)	18 (67)
	Asian	0 (0)	3 (11)
	Black	7 (26)	4 (15)
	Other	3 (11)	2 (7)
Extent of surgery	Unilateral	6 (22)	7 (26)
(n; %)	Bilateral	21 (78)	20 (74)
GMFCS (n; %)	Level IV	4 (15)	14 (52)
	Level 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) (n=46)		61 (30-86)	35 (23-68)
Left migration % (SD) (n=47)		46 (24-73)	44 (30.5-83.5)

Right acetabular index (SD) (n=45)	33 (26-40)	26.5 (19-33.5)
Left acetabular index (SD) (n=45)	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)

Summaries of PPP, CPCHILD and the parent/carer analogue scale are provided in Table 2; model-based estimated mean differences, p-values and 95% confidence intervals can be found in Table 3. The group differences in PPP were small at all time points (Table 2) and none, including at the primary end point, was found to be statistically significant (Table 3). The estimated standardised group difference at six weeks after randomisation was 0.11. The largest estimated difference was at two weeks after randomisation and was in favour of intervention, but there was no trend across all time points.

Table 2. Summaries of outcomes by treatment arm and time point.

Outcome	1 week		2 weeks		3 weeks		4 weeks		5 weeks		6 weeks	
	Botulinum toxin	**Placebo**	**Botulinum toxin**	**Placebo**	**Botulinum toxin**	**Placebo**	**Botulinum toxin**	**Placebo**	**Botulinum toxin**	**Placebo**	**Botulinum toxin**	**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)											57.60 (12.95)	55.24 (12.93)
Parent analogue scale (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)	2.29 (2.10)	2.65 (2.33)

Table 3. Estimated treatment differences by time since randomisation.

Outcome	1 week		2 weeks		3 weeks		4 weeks		5 weeks		6 weeks	
	EMD (95% CI)	**p-value**	**EMD (95% CI)**	**p-value**	**EMD (95% CI)**	**p-value**	**EMD (95% CI)**	**p-value**	**EMD (95% CI)**	**p-value**	**EMD (95% CI)**	**p-value**
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 toxin minus placebo)

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

There was slightly higher use of analgesics in the BTX-A arm (mean 68.7, SD 24.0) compared to placebo (mean 63.9; SD 17.7). The estimated difference was not 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 5 days (IQR 4-7) in BTX-A arm and 5 days (IQR 5-6) in placebo arm; z=-0.11, p=0.91), in time until return to school/day-care (median 34 days (IQR 22-49) in BTX-A arm and 38 days (IQR 28-43) in placebo arm; z=0.50), or ability to tolerate sitting at 6 weeks (median 240 minutes (IQR 210-420) in BTX-A arm and 300 minutes (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 BTX-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 BTX-A trial arm. There was one death in the placebo arm (n=1). Other events were prolonged hospital stay (n=5), hospitalisation (n=8), seizures (n=1) and pyrexia (n=1). There were 302 adverse events in total (n=156 in BTX-A toxin group). Of these, none were related to trial drug, and 219 were unremarkable postoperative findings. There was no evidence of a relationship between trial arm and intensity of AEs ($\chi 2$(2)=0.83, p=0.66).

Discussion

This was a randomised double-blind placebo-controlled trial to study the effect of preoperative BTX-A on post-operative pain in children with cerebral palsy. 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, i.e. 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 randomised placebo-controlled study of 16 children, Barwood et al recorded a reduction in pain following adductor release surgery if 8 units per kilogram of Botox® BTX-A was injected bilaterally into the adductor muscle area beforehand.[13] This was a small trial with no formal blinding, and the post-operative pain was measured by the nurses and trial coordinator using a score out of 3 and the post-operative analgesia that was given. Nevertheless we found it compelling enough to conduct a larger trial following more major surgery. In their study the muscles released at surgery had also been target by the trial drug, so we thought it clinically and methodologically sound to do the same.

In the Barwood cohort the BTX-A was injected 5-10 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 BTX-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 BTX-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 BTX-A.

The surgery conducted for the Barwood patients was considerably less extensive than for our patients, and they used double the dose of BTX-A spread over 2 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 post-operative period. BTX-A has been shown to be useful for pain management for the chronic pain of cerebral palsy.[11] A difference in post-operative pain might be detectable using a pain score designed for this purpose.

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

Protocol and trial registration

The trial protocol was published on the registry and results database of ClinicalTrials.gov (www.ClinicalTrials.gov; identifier: NCT01437644). The trial was registered on the European Clinical Trials Database: 2010-023240-33.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Contributors

E Will: first draft of the paper, revised by F Norman-Taylor, N Magill, C Lundy and G Doherty; collected standard clinical data, involved in study design
N Magill: statistical analysis and advice
R Ion: collected trial data and was trial co-ordinator
M Davies: collected trial data and was trial co-ordinator
G Doherty: involved in study design and input to paper
C Lundy: involved in study design and input to paper
A Roposch: involved in study design
C Fairhurst: involved in study design
F Norman-Taylor: Chief Investigator

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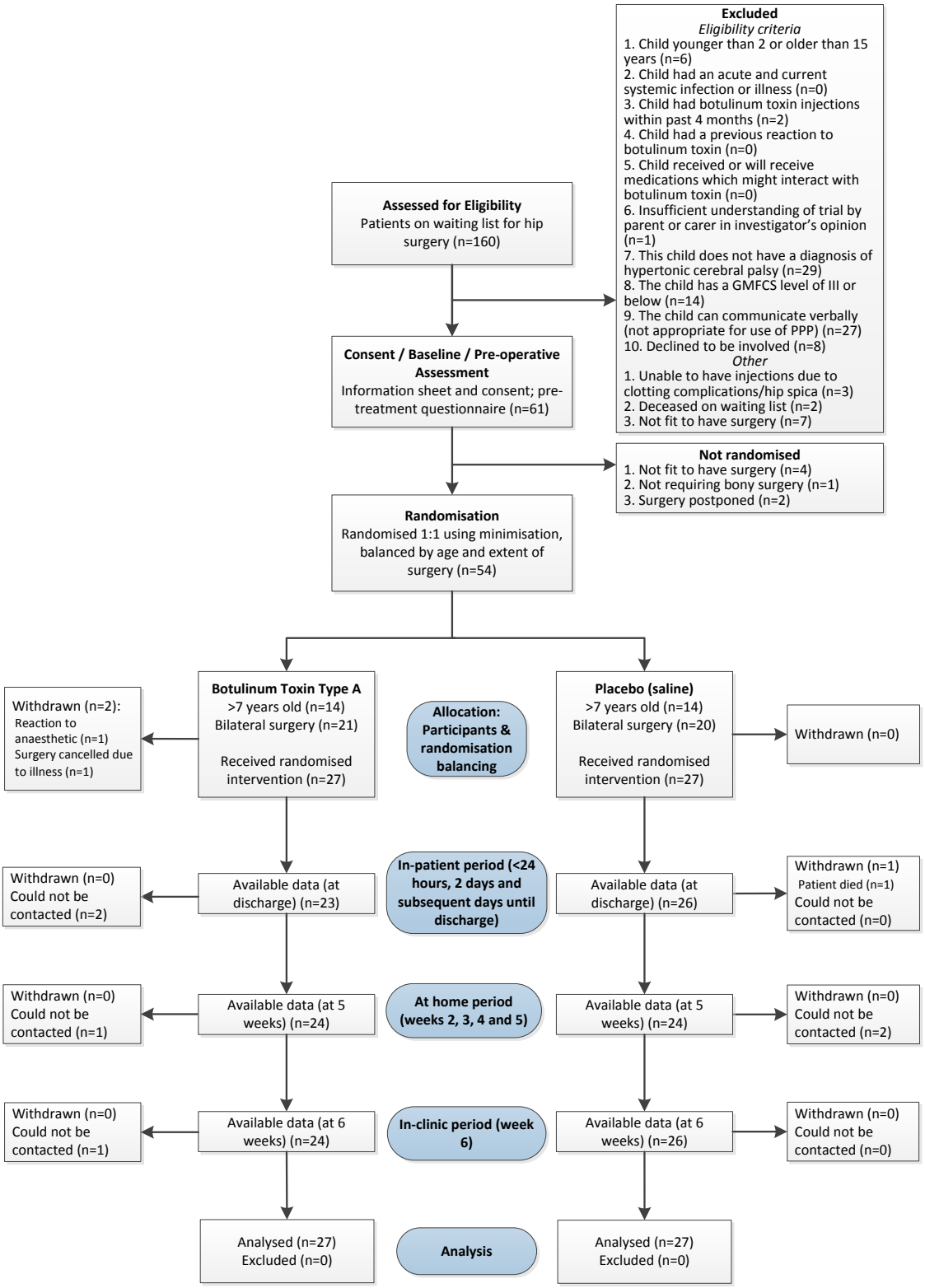

Figure 1. CONSORT diagram of POPPIES trial.