



Clinical trial results:

Post-operative pain in children with cerebral palsy following major hip surgery: a double blind randomised placebo controlled trial of pre-operative Botulinum toxin type A. [The Post-Operative Pain in cerebral Palsy (POPPIES) trial]

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2010-023240-33 |
| Trial protocol | GB |
| Global end of trial date | 07 January 2015 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 04 August 2019 |
| First version publication date | 04 August 2019 |
| Summary attachment (see zip file) | FINAL STUDY REPORT (Final Study Report.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | POPPIES |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01437644 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Guy's and St Thomas' NHS Foundation Trust |
| Sponsor organisation address | Great Maze Pond, London, United Kingdom, SE19RT |
| Public contact | Dr Fabian Norman-Taylor, Guy's and St Thomas' NHS Foundation Trust, 0044 020 7188 4658, fabian.norman-taylor@gstt.nhs.uk |
| Scientific contact | Dr Fabian Norman-Taylor, Guy's and St Thomas' NHS Foundation Trust, 0044 020 7188 4658, fabian.norman-taylor@gstt.nhs.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 07 January 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 January 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 January 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the benefit to children with cerebral palsy of having botulinum toxin injections prior to major hip surgery, in order to reduce their post-operative pain.

To describe the pain experience of children with cerebral palsy undergoing major hip surgery.

Protection of trial subjects:

A single dose of active drug or placebo was administered immediately prior to surgery.
The injections were given to the anaesthetised child before the surgical procedure began.

Background therapy:

None

Evidence for comparator:

None

| | |
|---|-------------------|
| Actual start date of recruitment | 21 September 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 54 |
| Worldwide total number of subjects | 54 |
| EEA total number of subjects | 54 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 26 |
| Adolescents (12-17 years) | 28 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from one clinical paediatric hospital in London between 2011 and 2015

Pre-assignment

Screening details:

Inclusion Criteria

1. The child has displaced hips requiring bony orthopaedic surgery (osteotomy) due to cerebral palsy
2. Is between the ages of 2 and 15 years (inclusive).
3. Has a GMFCS level of IV or V
4. Has a diagnosis of hypertonic cerebral palsy (or a diagnosis consistent with this nomenclature)
5. Does not communicate verbally

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer |

Blinding implementation details:

The surgeon or physician will administer medication in syringes containing the trial drug which he is unable to identify as active drug or placebo. The trial drug will be drawn up in six identical syringes for administration to the six muscle groups targeted with either 2 units per kilogram of Botulinum Toxin A or an equivalent volume of normal saline.

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | ACTIVE |

Arm description:

Injections of Botulinum neurotoxin A were given by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings and iliopsoas muscles on both sides, after the patient was (including anaesthetised on the day of surgery

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Botox® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

2 administration and units of Botox® per kilogram c at each site, up to a total of 50 units each site, and a total maximum of 300 units per child. Administered by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings and iliopsoas muscles on both sides, after the patient was anaesthetised on the day of surgery.

| | |
|------------------|---------|
| Arm title | PLACEBO |
|------------------|---------|

Arm description:

Injections of normal saline were given by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings and iliopsoas muscles on both sides, after the patient was (including anaesthetised on the day of surgery

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|------------------------|
| Investigational medicinal product name | Normal Saline |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

The volume of saline to be prepared per syringe is decided by referring to the study dosing chart and checking the volume related to the child's weight. This chart will be available to the pharmacist, study nurse and anaesthetist to double check in each case.

| Number of subjects in period 1 | ACTIVE | PLACEBO |
|---------------------------------------|--------|---------|
| Started | 27 | 27 |
| Completed | 24 | 26 |
| Not completed | 3 | 1 |
| Adverse event, serious fatal | - | 1 |
| Lost to follow-up | 3 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Trial | Total | |
|------------------------|---------------|-------|--|
| Number of subjects | 54 | 54 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| <7 years | 26 | 26 | |
| > 7 years | 28 | 28 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 23 | 23 | |
| Male | 31 | 31 | |

End points

End points reporting groups

| | |
|-----------------------|--------|
| Reporting group title | ACTIVE |
|-----------------------|--------|

Reporting group description:

Injections of Botulinum neurotoxin A were given by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings and iliopsoas muscles on both sides, after the patient was (including anaesthetised on the day of surgery

| | |
|-----------------------|---------|
| Reporting group title | PLACEBO |
|-----------------------|---------|

Reporting group description:

Injections of normal saline were given by the surgeon under ultrasound guidance into the adductor muscles, medial hamstrings and iliopsoas muscles on both sides, after the patient was (including anaesthetised on the day of surgery

Primary: Post-operative pain score using a validated numerical system (PPP).

| | |
|-----------------|--|
| End point title | Post-operative pain score using a validated numerical system (PPP). ^[1] |
|-----------------|--|

End point description:

The primary endpoint is the change in pain score during the six weeks following the operation. Pain will be measured using a validated questionnaire, the Paediatric Pain Profile. This scores pain by rating twenty different items of observed behaviour on an ordinal scale of 0 to 3 with a composite score of 0 to 60. It has been validated in children with severe cerebral palsy

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Until six weeks post operation.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Please see attached document for full results.

| End point values | ACTIVE | PLACEBO | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 27 | | |
| Units: whole | 24 | 27 | | |

| | |
|-----------------------------------|---------------------------------|
| Attachments (see zip file) | Results/POPPIES PUBLICATION.pdf |
|-----------------------------------|---------------------------------|

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary

| | |
|-----------------|-----------|
| End point title | Secondary |
|-----------------|-----------|

End point description:

Secondary endpoints

The following assessments will be made pre-operatively, at 6 weeks, at 3 months and at 6 months post-surgery:

- Clinical examination of the hips with measurement of ranges of movement
- X-ray measurement of hip displacement using the Migration Index (%), and dysplasia using the Acetabular Index (degrees).
- Quality of life using the CP-CHILD questionnaire

The following secondary endpoints will also be recorded:

- Immediate post-operative pain measured each day while in hospital by a simple parent (or carer) visual analogue scale (and continued weekly at home by the parents or carers for the first six weeks post-operatively with the help of the weekly telephone call).
- Drugs prescribed and given on the ward (from the drug chart).
- Length of hospital stay in days
- Estimated analgesia requirement by recall of analgesia use in the 24 hours prior to each weekly pain assessment during the weekly telephone call.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Until 6 weeks post operation. | |

| End point values | ACTIVE | PLACEBO | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 27 | | |
| Units: whole | 27 | 27 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

0 to six months post operation.

Adverse event reporting additional description:

Ongoing assessment during inpatient stay then follow up as out patient

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------|
| Reporting group title | BTX-A |
|-----------------------|-------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: 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 ($v2=0.83, p=0.66$).

| Serious adverse events | BTX-A | Placebo | |
|---|-----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 27 (22.22%) | 10 / 27 (37.04%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | 1 | 1 | |
| Surgical and medical procedures | | | |
| Hospitalisation - Chest Infection | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical replacement of loose screw in hip | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical repair of bony protrusion in hip joint | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Testes exploration -- de-torsion | | | |

| | | | |
|---|--|----------------|--|
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar Pontine Glioma | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 27 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypotension & Hypoxia during surgery | Additional description: Hip surgery abandoned post administration of anaesthesia and IMP due to hypoxia and hypotension. | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 27 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Hospitalisation - due to constipation | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 27 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hospitalisation - due to vomiting & dehydration | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Fracture Left arm | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 27 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Wound Infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hospital admission - Pyrexia | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Prolonged Hospitalisation - Urinary Tract Infection | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 27 (3.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | BTX-A | Placebo | |
|---|----------------|----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 27 (0.00%) | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30644541>