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Effectiveness and safety of early intramuscular botulinum toxin injections to prevent shoulder deformity in babies with brachial plexus birth injury (POPB-TOX), a randomised controlled trial: study protocol

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ABSTRACT

Introduction In children with brachial plexus birth injury (BPBI), denervation of the shoulder muscles leads to bony deformity in the first months of life, reducing active and passive range of motion (ROM) and causing activity limitation. The aim of this multicentre randomised controlled trial is to evaluate the effectiveness of botulinum toxin injections (BTI) in the shoulder internal rotator muscles of 12-month-old babies in limiting the progression of posterior subluxation of the glenohumeral joint, compared with a sham procedure mimicking BTI. The secondary aims are to evaluate the effectiveness of BTI in (1) limiting the progression of glenoid retroversion and three-dimensional (3D) deformity and (2) improving shoulder ROM and upper limb function, as well as to confirm the tolerance of BTI.

Methods and analysis Sixty-two babies with unilateral BPBI and a risk of posterior humeral head subluxation will be included. Only those with at least 7% posterior subluxation of the humeral head compared with the contralateral shoulder on the MRI will be randomised to one of two groups: 'BTI' and 'Sham'. The BTI group will receive BOTOX injections at the age of 12 months in the internal shoulder rotator muscles (8 UI/kg). The sham group will undergo a sham BTI procedure. Both groups will undergo repeated shoulder MRI at 18 months of age to quantify changes in the percentage of posterior migration of the humeral head (primary outcome), glenoid version and 3D bone deformity. Clinical evaluations (passive shoulder ROM, active movement scale) will be carried out at baseline and 15 and 18 months of age. The mini-assisting hand assessment will be rated between 10 and 11 months and at 18 months of age. Adverse events will be recorded at least monthly for each child.

Ethics and dissemination Full ethical approval for this study has been obtained. The findings will be disseminated in peer-reviewed publications.

Trial registration number EudraCT: 2015-001402-34 in European Clinical Trial database; NCT03198702 in Clinical Trial database; Pre-results.

Strengths and limitations of this study

- We expect botulinum toxin injections to limit shoulder deformity and improve shoulder range of motion in children with brachial plexus birth injury.
- This randomised controlled study will evaluate the safety and effectiveness of early botulinum toxin injections in the shoulder internal rotator muscles.
- The effect on bony deformities (glenohumeral subluxation and glenoid version), active and passive range of motion and upper limb function will be evaluated.

INTRODUCTION

Brachial plexus birth injury (BPBI) refers to injury to one or more cervical nerve roots (C5–C8) and/or the first thoracic nerve root (T1), usually caused by traction during a difficult birth. The incidence is around 1.5 per 1000 births.[1] In one-third of cases, nerve recovery is incomplete or absent,[1 2] resulting in permanent impairment which in turn may lead to activity limitation and participation as defined by the International Classification of Functioning.[3 4]

BPBI greatly affects the musculoskeletal development of the shoulder complex.[3 5 6] Deformities occur very early, within the months following birth[6–8] and gradually worsen with the child's growth.[7 9] Bony and joint deformities are caused by the partial denervation of the shoulder muscles, which results in an imbalance of the forces acting on the glenohumeral joint.[6 10] In particular, there is often a dominance of the internal rotator muscles.[11 12] Excess glenoid retroversion is typical, along with deformation of the glenoid

fossa. This allows posterior migration of the humeral head to occur, eventually progressing to complete subluxation.[6–8 13] These deformities increase the risk of early degenerative joint changes and pain during childhood and adulthood.[14 15] Active and passive shoulder range of motion (ROM) are also reduced, causing a vicious circle in which the muscles cannot contract effectively because of the bony deformities and altered lever arms.[9] These changes reduce the functional capacity and quality of life of children with BPBI.[16 17]

Botulinum toxin injections (BTI) are a common treatment to reduce muscle activity. This treatment is mostly used to treat spasticity in children, particularly in the case of cerebral palsy[18]; however, it may also be useful in children with BPBI,[19 20] combined with other treatments such as physiotherapy, occupational therapy, orthoses and, in some cases, surgery. The dominant internal shoulder rotator muscles are often targeted in order reduce the strength imbalance between agonist and antagonist muscles.[21] One study suggested that BTI might be useful to reduce posterior subluxation or dislocation of the shoulder in babies with BPBI.[22] BTI could also improve passive and active shoulder ROM and functional capacity.[20 23 24] BTI is a minimally invasive treatment that is well tolerated in young children.[25] When used prior to surgery, it could avert or reduce the complexity of surgical secondary orthopaedic procedures (eg, subscapularis release, latissimus dorsi and teres major transfers).[22 23] Although the results of studies of early BTI for BPBI are encouraging, most studies are retrospective, include small samples and do not have a control group. The current level of evidence is thus insufficient to make robust conclusions regarding the effectiveness of BTIs in children with brachial plexus birth injury.

Randomised controlled trials to evaluate the efficacy of early BTI and to confirm its tolerance in children with BPBI are therefore now warranted. With regard to the control treatment, a sham procedure mimicking BTI without injection is ethically more appropriate than an invasive placebo procedure because of the young age of the children involved.

Aims and hypotheses

Aims

The main aim of this study is to evaluate the effectiveness of BTI in the internal shoulder rotator muscles of 12-month-old babies in limiting the progression of posterior subluxation of the glenohumeral joint.

The secondary aims are (1) to compare the effectiveness of BTI with a sham treatment in limiting the progression of glenoid retroversion and three-dimensional (3D) glenoid deformity; (2) to compare the effectiveness of BTI with a sham treatment in improving active and passive joint ROM and upper limb function; (3) to assess the tolerance of BTI in babies with BPBI; (4) to evaluate the effects of BTI on muscle growth and fatty infiltration of the injected muscles, as well as muscle volume balance around the shoulder and (5) to determine the long-term effect of BTI on frequency and type of surgical interventions.

Hypotheses

Our primary hypothesis is that BTI will limit posterior subluxation of the glenohumeral joint in the BTI group compared with the Sham group.

We further hypothesise that the progression of glenoid retroversion and 3D deformities will be reduced, the active and passive ROM will be increased and that number of secondary surgical interventions will be reduced in the BTI group compared with the Sham group. The robust design of this study will confirm the results of previous uncontrolled studies, providing a strong level of evidence for BTI treatment. We also hypothesise that BTI will be well tolerated by the babies.[25] With regard to morphological changes following BTI, we expect slight atrophy to occur in the injected muscles, with some fatty infiltration[26] but no change in non-injected muscles, leading to an improvement in the volume balance of agonist and antagonist muscles.[27]

METHODS/DESIGN

Design

A randomised, multicentre, double-blind, controlled, parallel group, superiority trial will be performed (V.3, 17 January 2018). One group will receive BTI and the other will undergo a Sham procedure.

Ethics

Full ethical approval for this study has been obtained by the ethical committee Ouest 1 of Tours and Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). The trial has been registered in the European Clinical Trial database (EudraCT: 2015-001402-34) and Clinical Trial database (NCT03198702). All families will be given a written information letter detailing the study and parents or guardians will sign informed consent prior to the child's inclusion. Any modification or amendment to the protocol will be submitted to the ethical committees and ANSM for approval. After approval, investigators and trial participants will be informed of the changes by letter or email. All trial databases will also be updated.

Recruitment

The sponsor is CHRU Brest. Babies will be recruited from six French hospitals (CHRU Brest, Centre de Réadaptation pour enfant Flavigny-sur-Moselle, Hôpital National de Saint Maurice, CHU Saint-Etienne, CHU Nîmes, CHU Rennes), all of which are specialised in the management of children with brachial plexus palsy and have access to MRI. All doctors involved are skilled in BTI. Hospitals were selected by the study coordinator and sponsor based on their responses to a feasibility questionnaire. It is predicted that during the 29 months of inclusion, around 2590 children will be born with BPBI in France,[1] of whom

466 will left with sequelae.[1] This study will recruit 13.5% of these babies (62 patients over 29 months). The investigator in each of the specialist participating centres will inform clinicians in local maternity units about the study, and flyers and posters will be displayed in the reception areas of clinics and maternity units. Clinicians will be asked to refer babies with obstetric brachial plexus palsy to their nearest participating specialist centre and they will be provided with information leaflets to give to the parents. External advertising will also include a webpage on the Brest CHRU website. If inclusion goals are not achieved, more centres will be asked to participate.

A rehabilitation physician and/or a surgeon in each participating specialist centre will identify potentially eligible babies for the study during routine consultations. The protocol will be explained and proposed to parents of babies between 10 and 11 months of age who have a high risk of bony deformity. An information letter will be given to the parents. If the parents agree to their baby's participation, and the baby fulfils the inclusion criteria, he or she will be enrolled in the study for 7 months.

The inclusion criteria are male or female babies aged between 10 and 11 months with unilateral BPBI; at least one of the following risk factors for posterior subluxation of the humeral head: 10° less passive external ROM of the affected shoulder compared with the contralateral shoulder and/or a score below 6 on the Active Movement Scale (AMS) for shoulder external rotation and abduction, elbow flexion or supination; whose parents or guardians have signed the consent form. Babies with bilateral BPBI, microsurgery or shoulder muscle surgery planned between 12 and 18 months of age, contraindications to the use of botulinum toxin (hypersensitivity to botulinum toxin or the excipients used or myasthenia), contraindications to MRI (pace maker, metal implants, foreign metal body in the eye, etc), MRI not possible in the Paediatric Day Hospital setting because of contraindications to the premedication protocol or organisational constraints, parents inapt to provide consent for the participation of their child or parents under the age of 18 years will be excluded.

Study procedure

The study procedure is described in figure 1 and table 1.

At visit 1 (between 10 and 11 months of age), the parents or guardians will sign the informed consent form and the baby will be included. The physician or surgeon will carry out a physical examination and will collect sociodemographic data including history of BPBI in a brother or sister, overweight or obesity of the mother, any medical conditions during the pregnancy (eg, gestational diabetes), the birth procedure (caesarean section, vaginal delivery with epidural, induction of labour, instrumental delivery, shoulder dystocia, term and duration), birth weight and length and APGAR score.

Visit 2 (at 11 months of age) will involve MRI to confirm the diagnosis of bony deformity (the humeral head on the involved side must be at least 7% more posterior than the humeral head on the contralateral side). Once confirmed, randomisation will be carried out. This will ensure that only babies with verified glenohumeral deformity are included, since clinical tests are not sufficiently

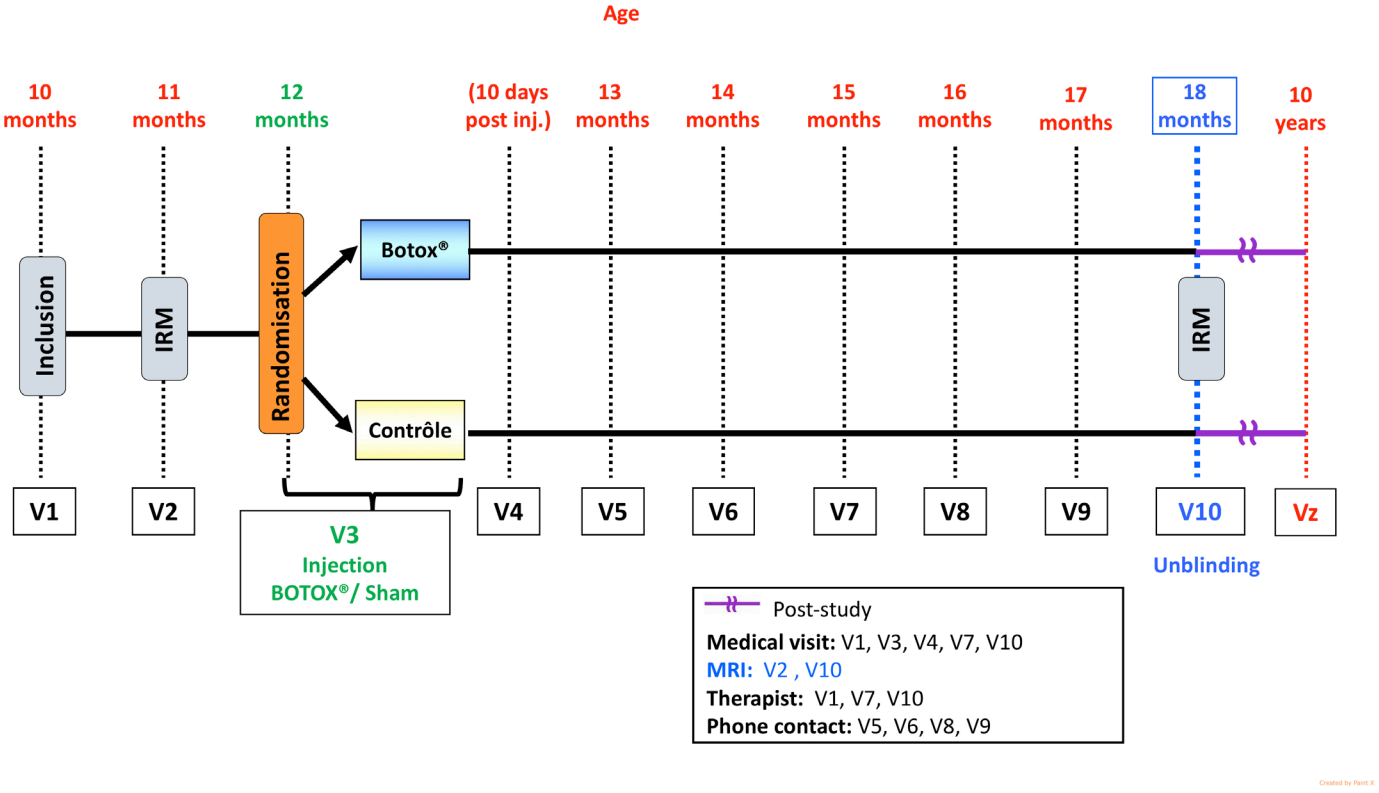

Figure 1 Flow chart.

Table 1 Visits and study procedure

Action	Visit 1 : 10 months of age (inclusion, medical and therapists)	Visit 2:11 months of age (MRI)	Visit 3:12 months of age (injection, medical follow-up I)	Visit 4: D10 post-injection (medical follow-up)	Visit 5:13 months of age (phone call)	Visit 6: 14 months of age (phone call)	Visit 7: 15 months of age (medical and therapists)	Visit 8: 16 months of age (phone call)	Visit 9: 17 months of age (phone call)	Visit 10:18 months of age (MRI, therapists medical)
Informed consent	*X*									
Inclusion/exclusion criteria	*X*									
Medical history	X									
Notification of existing and planned BPBI care	X*→									
Active and passive shoulder range of motion	X*→						X			X
Active movement scale	X*→						X			X
MRI of both shoulders		X								X
mini-AHA scale	X*→									X
Ramdomisation criterion		X								
Randomisation			X							
BTI or Sham procedure			X							
Notification of care (surgery or other)			X							
Establishment of standardised physiotherapy follow-up			X							
Follow-up of physiotherapy				X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Unblinding										X

X* →: will be carried out before MRI.
AHA, assistive hand assessment; BPBI, brachial plexus birth injury; BTI, botulinum toxin injection.

sensitive to confirm this. Babies who do not fulfil this randomisation criterion will be withdrawn from the study and will pursue the usual medical follow-up. The parents will be informed of the results of the MRI within 10 days by means of a telephone call from the research investigators. The randomisation will allocate the babies to one of two treatment groups (each with the same number of babies): BTI group and Sham group.

Visit 3 (12 months±15 days of age) will include treatment (BTI or Sham procedure).

Both groups will then attend seven follow-up visits: visit 4 will be carried out 10 days after treatment administration, and visits 6–10 will be carried out each month until 18 months of age. Visits 1, 7 and 10 will involve a standardised clinical examination by occupational therapists or physiotherapists and visits 5, 6, 8 and 9 will involve a telephone call from a member of the study team.

Unblinding will be performed at visit 10 (18 months of age). Following unblinding, the baby will attend a follow-up visit at 24 months then yearly follow-up visits, as is usual practice. The aim of this is to determine the safety of the use of botulinum toxin before the age of 2 years (after which there is a marketing authorisation for children with cerebral palsy) and to compare the frequency and complexity of surgical interventions between groups until the age of 10 years.

Magnetic resonance imaging

The babies included in this study will undergo MRI of both shoulders at visits 2 and 10 (at 11 and 18 months of age). A 3D, T1-weighted gradient-echo sequence will be used. This anatomical sequence highlights bones and muscles, including denervated muscles.[28] The child will lie supine with his/her arms in neutral and hands pronated. The T1 protocol[27] will be adapted in each centre depending on the type of MRI scan they have. Acquisition time will be less than 5 min per shoulder. No contrast injection will be required. Images will have to include sternum and spine medially, the whole deltoid laterally and the spine of the scapula at the back down. Premedication (sedation or general anaesthetic) will be necessary for both MRI examinations, at 11 and 18 months of age. The premedication will be adapted to the clinical status of each child and the customs of each centre. After premedication, the child will be monitored by a paediatrician in the day hospital of each centre using a validated protocol.

Randomisation process and blinding

Randomisation will be carried out using centralised computer randomisation by internet, according to the usual procedures in effect at Brest Regional University Hospital. After MRI confirmation that the baby fulfils the randomisation criterion (visit 2), randomisation will be performed by the study investigator on the day of the injection visit (visit 3, 12 months of age). Randomisation will be carried out via a specific dedicated website (https://chu-brest.hugo-online.fr/CSOnline/). This website is available 24 hours a day.

Stratification will be carried out by centre and by microsurgery prior to inclusion, since early surgery could influence the progression of bony deformity. Only the physician who will perform the BTI and the pharmacist will receive the email specifying the randomisation arm of each baby. Neither the parents or guardians nor the clinical and radiological evaluators will be aware of the treatment administered. The doctors carrying out the BTI will not take part in subsequent visits to ensure the blinding of the examiner. A central analysis of MRI data will be carried out in order to ensure blinding of the evaluator to the primary outcome measure.

Study treatments

BTI procedure

The botulinum toxin that will be used in the study is BOTOX (Allergan, Dublin, Ireland). Doses will be injected into the pectoralis major, subscapularis and teres major/latissimus dorsi muscles in a single site for each muscle on one occasion (visit 3: 12 months±15 days of age). These muscles have been the target of BTI treatment to prevent the progression of humeral head subluxation and to improve active and passive shoulder ROM in previous studies of children with BPBI.[22] Following reconstitution, the toxin will be injected intramuscularly using a transcutaneous approach with a 27 gauge, 25 mm long sterile needle. Ultrasound guidance will be used to identify the muscles. A detailed protocol has been written to ensure standardisation of the procedure (online supplementary file 1). The chosen doses are based on data in the literature in children and babies with BPBI[20 22 23]: a total of 8 U/kg will be injected (2 U/kg in subscapularis, 3 U/kg in pectoralis major and 3 U/kg in teres major/latissimus dorsi). Because there is no marketing authorisation for the use of botulinum toxin in children under the age of 2 years, the chosen doses are smaller than the maximal doses authorised for the treatment of spasticity in older children with cerebral palsy. Moreover, the doses chosen correspond with doses used in previous studies. A standardised protocol for the prevention and treatment of induced pain and postinjection pain will be systematically used. This will involve the administration of topical anaesthesia (such as EMLA) and paracetamol (dose according to the baby's weight) 1 hour prior to the injection. Distraction techniques will be used during the injection. The parents will be instructed to bring reassuring, familiar objects belonging to the baby (eg, soft toy, pacifier, nursery rhyme, music). In order to standardise practices and to ensure maximum safety and efficacy, staff from the different centres will all be trained in BTI of the shoulder muscles using ultrasound guidance in babies prior to participating in the study. Only physicians with at least 5 years of experience in BTI will be authorised to perform the injections.

Sham procedure

The aim of the Sham procedure is to mimic the BTI and to maintain the blinding of the research team and the

parents or guardians. The same anaesthetic procedure will be carried out as for BTI. The physician performing the injection will prepare a syringe containing physiological saline solution 10 min prior to the Sham procedure. The procedure will be simulated with ultrasound and use of a blunt needle (that will not penetrate the skin) on the sites selected for injection. All sites will be covered with adhesive dressings and tincture of betadine, as for the BTI. With regard to the control treatment, a Sham procedure mimicking BTI without injection is ethically more appropriate than an invasive placebo procedure because of the young age of the children involved.

Rehabilitation and medical follow-up

To ensure comparability, the babies in both groups will receive two sessions of physiotherapy per week. Physiotherapy will be standardised and based on evidence from studies of early physiotherapy management.[29 30] It will involve (1) maintaining passive ROM of all the upper limb joints, in particular shoulder external rotation, elbow extension and forearm pronation; (2) active-assisted and active movements of the involved shoulder; (3) bimanual functional training; (4) training to integrate the involved upper limb in functional activities and (5) parent education: child positioning, stimulation of active movement and function at home. A standardised medical prescription will be given. An information and advice letter will be given to the physiotherapists via the parents to standardise and optimise physiotherapy treatment. Advice will be given to parents regarding exercises to carry out at home; they will be taught to encourage use of the upper limb at home. All other medical treatment and rehabilitation will be carried out according to usual procedures.

Adverse events

Adverse events relating to the use of botulinum toxin

The secondary effects of BTI are mostly mild, temporary and related to the dose and the injection site. Local reactions such as contusions or pain at the injection site may occur, or excessive, localised muscle weakness. Systemic effects are rare and include generalised allergic reactions and effects related to product diffusion (rash, erythema, pruritus, anaphylactic reaction, flu-like syndrome, headaches, dizziness, fever, shivering, hypertension, and abdominal pain and dry mouth). Exceptionally, serious effects have been observed, a type of excessive muscle weakness, dysphagia and aspiration pneumonia; however, these occurred principally when the recommended doses were not respected.[25 31–33] The safety of BTI in infants under 2 years of age was shown to be good in a recent systematic review[25] and the tolerance of this treatment also seems good in this population.[22 33 34] The specific effects on muscle structure and the contractile properties of muscles are, however, poorly understood. Moderate muscle atrophy and fatty infiltration may occur following injections.[26 35 36]

According to the usual procedure used for the injection of botulinum toxin in each hospital, an information sheet will be provided to each patient explaining the action to be taken in the case of an adverse effect. According to this procedure, parents will be instructed to urgently consult their general practitioner or the paediatric emergency department in the case of the occurrence of a serious adverse effect such as generalised weakness or cardiorespiratory insufficiency. There is no antidote to botulinum toxin; therefore, symptomatic treatment will be administered, if required.

In the case of a serious adverse event, unblinding will be carried out. If an investigator wishes to treat the child with aminoglycosides, which are contraindicated in the case of treatment by botulinum toxin, unblinding will be carried out.

Parents will be questioned regarding adverse events at 10 days and then monthly between 12 and 18 months of age using standardised questionnaires that include all possible side effects.

Adverse events related to MRI premedication

The risks related to the premedication are the standard risks for the sedation or anaesthesia of children (gastritis, anticholinergic effects, oxygen desaturation, excessive sedation). The child will be examined for potential risks during a routine paediatric or anaesthetic consultation.

Independent data monitoring committee and unblinding procedure

An independent data safety monitoring committee (DSMC) composed of five independent members will be set up. The purpose of the DSMC will be to provide an independent evaluation of any adverse events that occur during the research, as well as to monitor the benefit/risk ratio.

Should an adverse event that requires different care than that planned in the study occur, unblinding will be carried out. Unblinding will not be carried out in any other condition.

Patient and public involvement statement

Patients were not involved in the development of the research and will not be involved in the recruitment and conduct of the study. Results of the study will be given to the parents after the study during a medical consultation in their participating centre.

OUTCOME MEASURES

Primary outcome

The primary outcome measure is the change in the percentage of posterior migration of the humeral head measured on an axial MRI image between 11 months (before the BTI at 12 months) and 18 months of age (6 months post-BTI) at visits 2 and 10 (table 1). Posterior subluxation will be evaluated using the method described by Waters, on an axial MRI slice taken just below the coracoid process.[37–39] Percentage posterior subluxation will be calculated in the following manner: a line will be traced from the medial border of the scapula to the

middle of the glenoid fossa. A segment will then be drawn perpendicularly to the line, from the widest part of the humeral head (AC). The length of the anterior part of this segment (AB) divided by the (AC) segment will be multiplied by 100 to obtain the percentage migration of the humeral head. A percentage below 50% indicates posterior migration of the humeral head. This measurement is quick to carry out and is used in both research and routine clinical practice in children and babies with BPBI to help preoperative decision-making for the type of intervention and postoperative follow-up.[6 8 39] Intrarater and inter-rater reliability have been shown to be excellent, with a 7% estimated measurement error.[38] MRI data will be analysed centrally (at Brest CHRU) by two trained investigators using the same guidelines in order to minimise inter-rater variability and to ensure the blinding of the evaluator.

Secondary outcome measures

Glenoid retroversion and 3D deformity

The following MRI measurements will be compared at visits 2 and 10 (11 and 18 months of age) (table 1) to determine the effectiveness of BTI relative to the Sham treatment in limiting the progression of glenoid retroversion and 3D deformity:

1. Two-dimensional (2D) glenoid version will be measured on an axial image using Friedman's technique.[40] This measurement has been validated and is used in clinical practice and research.[10 38]
2. 3D glenoid version and 3D migration of the humeral will be measured on MRIs following 3D reconstruction. These original measurements were recently used for the first time[41] and will provide an evaluation of 3D shoulder deformity and the effect of BTI on the deformity.

Passive and active movement and upper limb function

Three standardised evaluations will be carried out by occupational therapists or physiotherapists to compare the effect of BTI and the Sham treatment on active and passive joint ROM and upper limb function. All therapists will undergo training prior to their involvement in the study in order to ensure the reliability of measures.

1. Passive shoulder ROM will be measured at the baseline (before the MRI at visit 1, between 10 and 11 months of age), at visits 7 and 10 (15 months and 18 months of age visits).
2. The AMS will be rated at baseline (before the MRI at visit 1, between 10 and 11 months of age) and at visits 7 and 10 (15 months and 18 months of age visits). This test evaluates upper limb strength in babies with BPBI during active movements. Each movement is rated on an eight-point scale from 0 (no movement) to 7 (complete movement against gravity). It has satisfactory psychometric properties[42 43] in trained therapists.
3. The mini-assistive hand assessment (mini-AHA) will be rated at visits 1 and 10 (baseline and the 18 months of age visits). This functional evaluation measures bimanual performance during games and tasks. It was designed for children aged from 8 to 18 months.[44]

Tolerance

The parents of the babies in both groups will be questioned at 10 days and each month between 12 and 18 months of age using a standardised questionnaire that includes a list of all possible side effects of BTI.

Changes in muscle structure (BTI group only)

3D MRI reconstruction[27] and the validated technique described by Hogendoorn *et al*[45] will be used to respectively evaluate the direct effects of BTIs on muscle volume and fatty infiltration of the shoulder muscles. This evaluation will only be carried out in the BTI group.

Future surgical interventions

To determine if BTI reduces the frequency and complexity of surgical interventions in the long term, surgical procedures undergone by the children in both groups (recorded during routine medical follow-up) will be compared up to the age of 10 years.

Locations and data management

Each centre will manage their own recruitment of babies and organisation of MRIs, clinical evaluations and treatment. Electronic data will be secured and analysed in a central database managed by the Brest CHRU. Data will be the property of CHRU Brest.

In accordance with Good Clinical Practice (GCP) guidelines, the sponsor is in charge of obtaining agreement from all centres involved in the clinical research, in order to guarantee direct access to all the clinical research sites, to all the source data, source documents and all the reports for the purpose of quality control and audit by the sponsor.

All information required for the study will be entered in the paper case report forms (CRFs) during evaluations, then transferred to the electronic CRF (Clinsigth). Items of missing data will be coded. Each centre will be responsible for completing the CRFs for the babies enrolled in their centre. Each investigator will receive an instruction document regarding the use of this tool. The investigator will be responsible for the accuracy, quality and relevance of all the data entered. In addition, the data will be immediately verified as they are entered, using consistency checks. The investigator must validate any changes to the values in the CRF. These modifications will be subject to an audit trail. A justification can be added when applicable, as a comment. Data management and query processing will be carried out by a data manager.

A clinical research assistant (CRA) appointed by the sponsor will ensure the good running of the study, data collection on the paper CRF, data recording in the electronic CRF, data saving and reporting in accordance with the sponsor's standardised operating procedures as well as the GCP guidelines and current legislation and laws in force.

The investigator and the members of his/her team will agree to be available during all the routine and planned quality control visits by the CRA. During these visits, the following will be audited: signed informed consent, compliance with the study protocol and procedures, data recorded in the CRF: accuracy, missing data, consistency between these data and their 'source' (medical files, original laboratory results, etc), product management and investigator file. The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. Medical confidentiality cannot be invoked in opposition to these audits and inspections.

Any data sent to the sponsor by the investigators (or any other specialised parties) during or after the biomedical research will be anonymised. These data should not reveal any visibly accurate names and addresses of enrolled (involved) individuals. Only the first letter of the subject's name and first name will be saved along with a coded number indicating the order of inclusion of the subjects. The sponsor will ensure that the parent of each research subject has given permission in writing for access to personal information about the baby which is strictly necessary for the quality control of the research.

Sample size and statistical analysis

No longitudinal data regarding the progression of bony deformities in children with BPBI are available in the literature. Only transversal studies have been carried out, indicating that posterior subluxation is significantly greater on the affected side compared with the healthy side at the age of 4.8 months (affected side 32.1%—: SD=19.7% vs healthy side 49.8%: SD=7.3%).[6] The calculation of the number of subjects necessary for this study was based on a difference of the standard deviation at 12 months, for a SD of 5%.

In order to guarantee a power of 90%, a sample of 22 babies per group is required, thus a total of 44. In order to account for babies lost to follow-up (10%) and babies who will not be treated because of a lack of true subluxation on MRI, 62 babies will be recruited.

The characteristics of the babies in both groups will be described using means, SD, medians, quartiles or frequencies. Mean changes in 2D percentage humeral subluxation, 3D humeral subluxation, 2D and 3D glenoid version, the AMS score and passive shoulder ROM will be compared using analysis of covariance (ANCOVA) adjusted on the initial values. If the hypotheses underlying the ANCOVA model are not respected, a non-parametric Wilcoxon test will be used. Shoulder muscle volumes and the mini-AHA scores will be compared between the groups using a Student's t-test or a non-parametric Mann-Whitney test, depending on the distribution of the variable of interest. Lastly, the number of serious and non-serious adverse events, and the degree of fibrosis and fatty infiltration will be compared between the two groups using a χ^2 test or Fisher's exact test, so as the number of secondary surgeries. $P<0.05$ will be considered as statistically significant.

Data analysis will be carried out on an intention to treat basis by a biostatistician after blind review and database freezing at the end of the study. No intermediate analysis is planned during this trial.

DISCUSSION

This paper presents the background and design for a multicentre double-blind randomised controlled trial to evaluate the effectiveness of BTI in the shoulder internal rotator muscles of 12-month-old babies in limiting the progression of posterior subluxation of the glenohumeral joint, compared with a sham procedure. To our knowledge, this is the first study with a sufficiently robust methodology to allow conclusions to be based on a high level of evidence.

The babies included in the study will all receive two sessions of physiotherapy per week. This choice was made because it is usual practice for babies with BPBI in France. In addition, studies in other pathologies have shown that physiotherapy potentiates the effectiveness of BTI.[46] Casting will not be used because it is invasive, has a low level of evidence and comports a risk of interference with motor development in children who already have central nervous system abnormalities.[47]

The primary endpoint, change in the percentage posterior migration of the humeral head measured on an axial MRI image between 11 months (before BTI) and 18 months of age (6 months post-BTI), was chosen for its clinical relevance and its strong psychometric properties compared with clinical or functional assessments in this population. Because the aim of this study is to evaluate both bone deformity and muscle morphology in order to document the consequences of BTI in non-spastic muscles and on shoulder muscle balance, we preferred MRI over ultrasound since MRI can accurately measure both elements while ultrasound cannot.

Clinical evaluations carried out before and after BTI will determine the effects of the treatment on shoulder ROM and functional capacity. Evaluations will be carried out monthly, with alternate phone contacts and direct consultations in order to limit travelling, promote adherence and limit losses to follow-up. Because there is currently no marketing authorisation for BTI in infants under the age of 2 years, special attention was paid to the safety assessment. The use of a systematic and detailed questionnaire will yield detailed and specific data, confirming or not the safety of BTI before the age of 2 years.

Glenohumeral dysplasia can occur as early as 3 months of age. If this trial has positive results and if the safety of BTI performed at 12 months of age in children with BPBI is proven, studies evaluating the effect of BTI in the limitation of glenohumeral deformity in younger babies could be warranted.

The results of the study could lead to a request for an evaluation by the French National Agency for Medicines and Health Products Safety for Temporary Recommendation for Use of botulinum toxin in children with BPBI. It is expected that the results of this trial will be published in peer-reviewed scholarly journals and international academic conferences. After the trial, if positive results are highlighted in the children who had BTIs, the treatment will be proposed to the children in the sham group. These children will, however, be older and the efficacy may be lower, especially for the bone deformity.

CONCLUSION

The POPB-TOX trial is a nationwide, multicentre, randomised, controlled study that will evaluate the effectiveness of BTI in the internal shoulder rotator muscles of 12-month-old babies with BPBI in limiting shoulder deformity. Tolerance of the treatment will also be determined. Existing results from uncontrolled studies suggest this treatment may be effective; however, the present study will allow robust conclusions to be drawn, potentially leading to a change in the care of these children.

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Contributors CP and SB conceived the study and defined the original study protocol. CP, FF, NQ and SB developed the intervention parameters. MG and DBS defined the radiological parameters and developed radiological protocols. DE is responsible for the ethics applications and the ethical reporting of the study. CP, LH, FF and NQ are responsible for recruitment, data collection and implementation of the study. GLG is responsible for the study methodology. POPB-tox group involves physicians who are only implicated for recruitment and data collection. All authors have read and approved the final manuscript. CP, DE and SB drafted the final version of this manuscript.

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