PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and safety of early intramuscular botulinum toxin injections to prevent shoulder deformity in babies with brachial plexus birth injury (POPB-TOX), a randomized controlled trial: study protocol
AUTHORS	Pons, Christelle; Eddi, Dauphou; Le Gal, G.; Garetier, Marc; Ben Salem, Douraied; Houx, Laetitia; Fitoussi, Franck; Quintero, Nathaly; Brochard, Sylvain; POPBtox group, POPBtox group

VERSION 1 – REVIEW

REVIEWER	Xiao Bao Department of rehabilitation Medicine, Yue Bei People's Hospital, ShaoGuan, China
REVIEW RETURNED	04-Oct-2018

GENERAL COMMENTS	Study is well designed in all areas. Authors want to demonstrate effect and safety of intramuscular botulinum toxin injections to prevent shoulder deformity in babies with obstetrical brachial plexus palsy. However, some questions and corrections should be response. 1. corrections needed: "OBBP" should be "OBPP" in line 4 on page 6. 2. questions You write "Randomisation will be possible 24 hours per day using centralised computer randomisation by Internet". I suggest to clarify how to randomize in detail. How do you ensure the safety of botulinum toxin for baby under 2 years age. If occur toxic symptom or allergic symptom, how do you deal with them? You write "The botulinum toxin that will be used in the study is BOTOX (Allergan)". I suggest more BOTOX information is needed, such as company, county. You should clarify the ultrasound guidance process, such as position, sterile operation, Syringe model. Some more scientific information is needed to describe the rehabilitation therapy after injections. In general, botulinum toxin injections could be one site one muscle or muti-site one muscle. What about your injections? Please add it.

REVIEWER	Dan Zlotolow United States
REVIEW RETURNED	06-Feb-2019

GENERAL COMMENTS	General Comments: Please change the name of the diagnosis to Brachial Plexus Birth Injury (BPBI) as per consensus vote from Plexus Nexus 2017. OBPP can have legal implications for the obstetrician. The line numbers do not match up with the lines, and they are not continuous, making it impossible to assign specific comments. Please resubmit the article with sequential line numbers that relate to the lines of text. "Excessive" is a legal term that refers to unwarranted traction being placed on the brachial plexus during delivery. Please avoid this term. The study protocol is flawed for many reasons. 1) I do not believe that there is equipoise to consider using a placebo treatment. Several studies have now shown botox and casting to improve clinical outcomes, and our experience bears this out. 2) It is very difficult to accurately inject botox into specific muscle in a screaming, writhing 11 month-old. Previous studies performed the Botox injection under general anesthesia. 3) Patients will not be casted after botox injection, which is currently the standard of care and may be the catalyst for improvement. 4) The age of the patients is too late and uniform. Some children develop glenohumeral dysplasia as early as 3 months of age. 11 months may be too late for some children to obtain a closed reduction. 5) Ultrasound has been shown to be a good screening tool for glenohumeral dysplasia, and at-risk children should get serial ultrasounds as early as 3 months every 3 months until 1 year of age or until the child demonstrates progressive or moderate glenohumeral dysplasia. At that time, botox is indicated. 6) AMS has not been validated as an outcomes measure across therapists or across institutions, only for two surgeons at the same institution with similar training and familiarity. A consensus session to train all the therapists with live patients should be carried out as per Bae et al AMS validation study. Video examinations may also be considered and graded by a consensus group. I therefore suggest the following alternate protocol: 1. Patients should be screened with ultrasound for glenohumeral dysplasia at 3 months of age and every 3 months thereafter up to 12 months of age. As soon as the child displays moderate or progressive glenohumeral dysplasia, 1)Botox AND shoulder spica casting with the arm in adduction and maximal external rotation and forearm in neutral OR 2) placebo AND casting OR 3) Botox without casting should be performed. This should be done with ultrasound guidance and/or electrical stimulation with an insulated needle under general anesthesia. 2. The cast should stay on for 4 weeks. If there is sufficient power, consider further randomization to a night-time brace following the casting for a further 3 months. 3. Use photographs to document passive range of motion in adduction and external rotation and abduction and external rotation with a standardized method preop and postop.

	4. Use a video mallet with 2 orthogonal cameras to record the AMS and (after 2 years of age) the Mallet. 5. Obtain an MRI preop and at 2 years of age.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Xiao Bao
Institution and Country: Department of rehabilitation Medicine, Yue Bei People's Hospital, ShaoGuan, China

Study is well designed in all areas. Authors want to demonstrate effect and safety of intramuscular botulinum toxin injections to prevent shoulder deformity in babies with obstetrical brachial plexus palsy. However, some questions and corrections should be response.

1.corrections needed:
"OBBP" should be "OBPP" in line 4 on page 6.

We apologise for this mistake. According to the comment by the 2nd reviewer, we changed the name of the diagnosis to Brachial Plexus Birth Injury or BPBI.

2.questions
You write "Randomisation will be possible 24 hours per day using centralised computer randomisation by Internet". I suggest to clarify how to randomize in detail.

Thank you for this comment. We clarified that: "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). Randomization 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 randomization arm of each child."

How do you ensure the safety of botulinum toxin for baby under 2 years of age. If occur toxic symptom or allergic symptom, how do you deal with them?

We thank the reviewer for raising this important point. 7/16/2019 10:40:00 AMWe enriched the paragraph regarding adverse events relating to the use of botulinum toxin: "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 pediatric emergency department in the case of the occurrence of a serious adverse effect such as generalized weakness or cardio-respiratory 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 standardized questionnaires that include all possible side effects ."

You write “The botulinum toxin that will be used in the study is BOTOX (Allergan)”. I suggest more BOTOX information is needed, such as company, county.

We have added this information: BOTOX (Allergan, Dublin, Ireland).

You should clarify the ultrasound guidance process, such as position, sterile operation, Syringe model.

Thank you for your comment. We added some details in the text and propose to provide a supplementary material describing precisely the Botulinum toxin injections procedure (supplementary material 1): “Following reconstitution, the toxin will be injected intramuscularly using a transcutaneous approach using a 27 gauge, 25mm long sterile needle. Ultrasound guidance will be used to identify the muscles. A detailed protocol was written to ensure standardization of the procedure (supplementary material 1).

Supplementary material 1: Botulinum toxin injections procedure

The Botox will be injected intramuscularly by transcutaneous approach using a 27 gauge, 25mm long sterile needle. This information can be added in the main text.

In the study protocol, we specifically described the procedure to ensure standardization (provided below). We propose to add this as supplementary material in the article.

“One hour before the injections, preliminary ultrasound identification will be carried out so that anaesthetic cream can be applied to the skin over the future injection sites.

For all injections, the child will be held in the arms of one of his/her parents.
Teres Major:
The parent will recline on the examination table, with the baby in his/her arms facing him/her (“belly to belly”). The sleep mask will be positioned on the parent at this time to ensure the blinding. The paediatric auxiliary can help to hold the child if necessary. The teres major muscle will be located by ultrasound, and the skin disinfected. Injection and/or simulation of the injection of the muscle (sham procedure) will be performed using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing. Subscapularis:
The baby will remain in the arms of the parent, "belly to belly". The arm on the injected side will be placed in maximum abduction by the paediatric auxiliary. The subscapularis muscle will be identified by ultrasound. The skin will be disinfected. Injection and/or simulation of the injection of the muscle will be performed (sham procedure) using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.
Pectoralis Major:
The face mask will be removed so that the parent can change position and the position of the baby can be changed. The parent will sit in a chair with the child on his/her lap in a sitting position. The face mask will be repositioned. The pectoralis major muscle will be identified by ultrasound. The skin will be disinfected. Injection and/or simulation of the injection of the muscle (sham procedure) will be performed using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.”

Some more scientific information is needed to describe the rehabilitation therapy after injections.

Thank you for your comment. We described the rehabilitation therapy: “To ensure comparability, the babies in both groups will receive 2 sessions of physiotherapy per week. Physiotherapy will be standardized and based on evidence from studies of early physiotherapy management [29,30]. It will involve: (I) maintaining passive range of motion of all the upper limb joints, in particular shoulder external rotation, elbow extension and forearm pronation; (II) active-assisted and active movements of the involved shoulder; (III) bimanual functional training; (IV) training to integrate the involved upper limb in functional activities and (V)
parent education: child positioning, stimulation of active movement and function at home.”

In general, botulinum toxin injections could be one site one muscle or muti-site one muscle. What about your injections? Please add it.

This was added: “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: 12months +/- 15 days of age).”

Reviewer: 2
Reviewer Name: Dan Zlotolow
Institution and Country: United States
Please state any competing interests or state ‘None declared’: none

General Comments:

Please change the name of the diagnosis to Brachial Plexus Birth Injury (BPBI) as per consensus vote from Plexus Nexus 2017. OBPP can have legal implications for the obstetrician.

We apologize for this mistake. This was changed.

The line numbers do not match up with the lines, and they are not continuous, making it impossible to assign specific comments. Please resubmit the article with sequential line numbers that relate to the lines of text.

This was changed.

"Excessive" is a legal term that refers to unwarranted traction being placed on the brachial plexus during delivery. Please avoid this term.

We apologise for this wrong utilization of « excessive ». It has been removed: “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 .”

The study protocol is flawed for many reasons.

1) I do not believe that there is equipoise to consider using a placebo treatment. Several studies have now shown botox and casting to improve clinical outcomes, and our experience bears this out.

We understand the issue raised by the reviewer. However none of the studies of the effects of botulinum toxin injections are controlled (Ezaki et al. 2010; Gobets et al. 2010; Michaud et al. 2014).

Most are retrospective case series. Thus, we believe that the current level of evidence is insufficient to make robust conclusions regarding the effectiveness of botulinum toxin injections in children with brachial plexus birth injury.
Another issue is that in France, the use of botulinum toxin to treat this pathology is not currently possible because there is no marketing authorization. One step to obtain such an authorization is by carrying out a randomized controlled study to demonstrate the benefits of botulinum toxin injections in this population.

We highlighted this point in the introduction: “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 botulinum toxin injections in children with brachial plexus birth injury. ” and in the discussion “The results of the study could lead to a request for an evaluation by the French National Agency for Medicines and Health Products Safety (ANSM) for Temporary Recommendation for Use (TRUs) of botulinum toxin in children with BPBI. ”; “The POPBTOX 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.”

2) It is very difficult to accurately inject botox into specific muscle in a screaming, writhing 11 month-old. Previous studies performed the Botox injection under general anesthesia.

We agree with the reviewer that performing BTI injections in a 12 month-old baby is difficult. This was anticipated in the protocol and the procedure was validated by external research committees. Only physicians with at least five years of experience in BT injections will be authorized to perform the injections. In France the vast majority of BTI are performed without general anaesthesia even in small children (2 years old) (Chaléat-Valayer et al. 2011) and the physicians are familiar with this procedure. In order to ensure the injection is rapid, ultrasound identification will used before BTI for the application of the anaesthetic cream as well as during BTI. Moreover the child will be held by a parent for reassurance and the physician will be helped by a nurse and paediatric auxiliary during the procedure.
Some children have already been included in the study. So far, all injections have been performed with success.
We detailed this in the text: “In order to standardize 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 five years of experience in BTI will be authorized to perform the injections. ” and we propose to provide the protocol describing botulin toxin injections procedure (with description of the participation of the nurse and paediatric auxiliary) in supplementary material 1.

3) Patients will not be casted after botox injection, which is currently the standard of care and may be the catalyst for improvement.

We agree that BTI alone may be insufficient, as has been shown in populations of children in which BTI are used in clinical practice, and that this is an interesting research question. However, the current evidence for the association of BTI and casting in children with brachial plexus birth injury is not compelling (Gobets et al. 2010; Michaud et al. 2014). We only found one protocol “An early shoulder repositioning program in birth-related brachial plexus injury : a pilot study of the sup ER protocol”(Verchere et al. 2014) that evaluates this, with only

preliminary results for now.
Thus, because of the invasive nature of casts, and the risk of interference with motor development in children who already have central nervous system abnormalities (Anguelova et al. 2017), we chose not to use casts.
Moreover, to potentiate the effect of BTI, physiotherapy will be systematically prescribed and parents will be taught to encourage use of the upper limb at home.

We added some details in the discussion section “The babies included in the study will all receive 2 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].”

4) The age of the patients is too late and uniform. Some children develop glenohumeral dysplasia as early as 3 months of age. 11 months may be too late for some children to obtain a closed reduction.

Studies in children older than one year (Gobets et al. 2010) showed positive results after botulinum toxin injections regarding range of motion. Our hypothesis is that the greater mobility of the shoulder and decrease in abnormal mechanical constraints following BTI will limit the progression of glenohumeral dysplasia compared to the children who undergo the placebo injection. We will be able to verify this hypothesis by measuring both glenohumeral deformity and active and passive range of motion.
Furthermore, the National drug administration did not allow us to include younger children.

To highlight these points, we added one paragraph in the discussion: “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 gleno-humeral deformity in younger babies could be warranted.”

5) Ultrasound has been shown to be a good screening tool for glenohumeral dysplasia, and at-risk children should get serial ultrasounds as early as 3 months every 3 months until 1 year of age or until the child demonstrates progressive or moderate glenohumeral dysplasia. At that time, botox is indicated.

We agree that ultrasound is useful for the evaluation of glenohumeral dysplasia. However, we planned to evaluate both bone deformity and muscle morphology in order to document the consequences of BTI in non-spastic muscles and in the shoulder muscle balance. We chose to use MRI because it can measure both these elements, while ultrasound cannot.
Because all the studies of botulinum toxin injections are uncontrolled or retrospective case studies (Ezaki et al. 2010; Gobets et al. 2010; Michaud et al. 2014), we are convinced of the necessity of a randomized controlled trial with a placebo intervention. Methodologically, it is not feasible to include children of different ages while keeping comparable groups for this study.
However, we agree that serial ultrasounds would be very useful in clinical practice if the benefit of BTI is demonstrated in children with brachial plexus injury.

We specified that in the discussion: “Because the aim of this study is to evaluate both bone deformity and muscle morphology in order to document the consequences of BTI in nonspastic muscles and on shoulder muscle balance, we preferred MRI over ultrasound since MRI can accurately measure both elements while ultrasound cannot”.

6) AMS has not been validated as an outcomes measure across therapists or across institutions, only for two surgeons at the same institution with similar training and familiarity. A consensus session to train all the therapists with live patients should be carried out as per Bae et al AMS validation study. Video examinations may also be considered and graded by a consensus group.

Thank you for this pertinent suggestion. We will carry out video-recordings of the test for grading by consensus.

We wish to point out, however, that the AMS is a secondary criterion. Because of the difficulty to evaluate very young children, we chose to use the change in the percentage posterior migration of the humeral head measured on an axial MRI as primary endpoint. This measure has strong psychometric properties compared with clinical or functional assessments.

I therefore suggest the following alternate protocol:
1. Patients should be screened with ultrasound for glenohumeral dysplasia at 3 months of age and every 3 months thereafter up to 12 months of age. As soon as the child displays moderate or progressive glenohumeral dysplasia, 1)Botox AND shoulder spica casting with the arm in adduction and maximal external rotation and forearm in neutral OR 2) placebo AND casting OR 3) Botox without casting should be performed. This should be done with ultrasound guidance and/or electrical stimulation with an insulated needle under general anesthesia. 2. The cast should stay on for 4 weeks. If there is sufficient power, consider further randomization to a night-time brace following the casting for a further 3 months.
3. Use photographs to document passive range of motion in adduction and external rotation and abduction and external rotation with a standardized method preop and postop.
4. Use a video mallet with 2 orthogonal cameras to record the AMS and (after 2 years of age) the Mallet.
5. Obtain an MRI preop and at 2 years of age.

We thank the reviewer for these suggestions.
Firstly, we would like to highlight the fact that the study was conceived with a methodologist and then validated and approved by national French agencies: the Ministry of Research, the National Ethical Committee and the National Drug Administration. Moreover, funding was granted by French national PHRC (Protocole Hospitalier de Recherche Clinique). The study protocol has therefore already been subjected to rigorous checks. Equally, the first reviewer approved the design. 7 children have already been included and the protocol was safe and feasible for these children.

It is thus not possible at this stage in the process to make major alterations to the protocol (ultrasound evaluation, botulinum toxin injections under general anesthesia, MRI at 2 years of age). We hope that the editor and the reviewers understand this point and that we convinced for the choices which were made with the answers to the 2nd reviewer's commentaries.

Regarding casts, there is currently insufficient evidence to justify their use in young children with brachial plexus injury. Because of the invasive nature of casts and the risk of interfering with motor development in children who already have central nervous system abnormalities, we chose to associate BTI with physiotherapy.

We thank the reviewer for his proposition to improve the AMS evaluation. We will use this for future inclusions.

We modified the article to justify the choices which were made throughout the text.

Anguelova, Galia V., Erwin de Vlugt, Alistair N. Vardy, Erik W. van Zwet, J. Gert van Dijk, Martijn J. A. Malessy, and Jurriaan H. de Groot. 2017. “Cocontraction Measured with ShortRange Stiffness Was Higher in Obstetric Brachial Plexus Lesions Patients Compared to Healthy Subjects.” Journal of Biomechanics 63 (October): 192–96. https://doi.org/10.1016/j.jbiomech.2017.08.015.
Chaléat-Valayer, Emmanuelle, Bernard Parratte, Cyrille Colin, Angélique Denis, Séverine Oudin, C. Bérard, J. C. Bernard, et al. 2011. “A French Observational Study of Botulinum Toxin Use in the Management of Children with Cerebral Palsy: BOTULOSCOPE.” European Journal of Paediatric Neurology: EJPN: Official Journal of the European Paediatric Neurology Society 15 (5): 439–48. https://doi.org/10.1016/j.ejpn.2010.04.006.
Ezaki, Marybeth, Kanchai Malungpaishrope, Richard J. Harrison, Janith K. Mills, Scott N. Oishi, Mauricio Delgado, Patricia A. Bush, and Richard H. Browne. 2010. “Onabotulinum ToxinA Injection as an Adjunct in the Treatment of Posterior Shoulder Subluxation in Neonatal Brachial Plexus Palsy.” The Journal of Bone and Joint Surgery. American Volume 92 (12): 2171–77. https://doi.org/10.2106/JBJS.I.00499.
Gobets, David, Heleen Beckerman, Vincent de Groot, Miriam H. Van Doorn-Loogman, and Jules G. Becher. 2010. “Indications and Effects of Botulinum Toxin A for Obstetric Brachial Plexus Injury: A Systematic Literature Review.” Developmental Medicine and Child Neurology 52 (6): 517–28. https://doi.org/10.1111/j.1469-8749.2009.03607.x.
Michaud, Linda J., Emily J. Louden, William C. Lippert, Allison J. Allgier, Susan L. Foad, and Charles T. Mehlman. 2014. “Use of Botulinum Toxin Type A in the Management of Neonatal Brachial Plexus Palsy.” PM & R: The Journal of Injury, Function, and Rehabilitation 6 (12): 1107–19. https://doi.org/10.1016/j.pmrj.2014.05.002.
Verchere, Cynthia, Kim Durlacher, Doria Bellows, Jeffrey Pike, and Marija Bucevska. 2014. “An Early Shoulder Repositioning Program in Birth-Related Brachial Plexus Injury: A Pilot Study of the Sup-ER Protocol.” Hand (New York, N.Y.) 9 (2): 187–95. https://doi.org/10.1007/s11552-014-9625-y.

VERSION 2 – REVIEW

REVIEWER	Xiao Bao Hospital in China
REVIEW RETURNED	08-Aug-2019

GENERAL COMMENTS	Study is well designed in all areas. authors hypothesized botulinum toxin injections could limit shoulder deformity and improve shoulder range of motion in children with brachial plexus birth injury. Minor suggestions: If BTI could limit shoulder deformity and improve shoulder range of motion in children with brachial plexus birth injury, Author should state how to treat the sham group after the experiment.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Xiao Bao
Institution and Country: Hospital in China
Please state any competing interests or state 'None declared': None declared

Study is well designed in all areas. authors hypothesized botulinum toxin injections could limit shoulder deformity and improve shoulder range of motion in children with brachial plexus birth injury.
We thank the reviewer for his comment.

Minor suggestions:
If BTI could limit shoulder deformity and improve shoulder range of motion in children with brachial plexus birth injury, Author should state how to treat the sham group after the experiment.
Thank you for this comment.
We added one sentence "After the trial, if positive results are highlighted in the children who had botulinum toxin injections, 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."