Pediatric Eye Disease Investigator Group

Esotropia Treatment with Botulinum Toxin-A Injection Data Collection (E02)

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1.0 Introduction

1.1 Background

Esotropia is a common condition in childhood, occurring in approximately 2% of all children under 6 years of age.[1] Traditional incisional surgery using bilateral medial rectus muscle recession (BMR) has been the mainstay of treatment for childhood esotropia. However, a number of studies in the literature suggest that injection of both medial rectus muscles with botulinum toxin type A (BTX-A) is also an effective treatment.[2-17]

BTX-A decreases skeletal muscle force generation by blocking release of acetylcholine into the synaptic cleft of neuromuscular junctions, creating a temporary chemical denervation of treated muscle. Onset of treatment effect is seen at approximately 3 days post-injection and remains maximal until onset of recovery at approximately 6 weeks. Full recovery of treated muscles is normally seen at about 3 months, at which time reinjection can be considered if needed. The potential advantages of BTX-A as an alternative to traditional surgery include reduced scarring, preservation of the biomechanical relationships of the medial rectus muscles with the globe and with soft-tissue pulleys in the orbit, the potential for improved sensory outcomes,[13, 16-18] decreased incidence of latent nystagmus and DVD,[12, 15] dramatic reduction in the incidence of consecutive exotropia,[2, 16, 18] and decreased operative time. BTX-A injection may require up to 10 minutes compared with up to one hour for incisional muscle surgery. Decreased procedure time also translates into less anesthesia time. Recognized risks of treatment with BTX-A include globe perforation, ptosis and transient vertical deviations with the subsequent risk of amblyopia,[3-6, 15, 16] extraocular muscle injury, hemorrhage, and collateral deleterious effects on surrounding extraocular muscles. Overall, the risk of a vision-threatening complication of BTX-A injection is felt to be low and not substantially different from traditional incisional surgery.

There are few rigorous data on motor alignment outcomes after treatment of small to moderate-angle esotropia with a single injection of BTX-A, with success rates varying widely from 34% to 88%.[10, 13, 15, 16, 19] Some data is available from a prospective study by McNeer et al[10] which evaluated children with infantile esotropia (IET). Of subjects who were injected with 2.5 units of BTX-A before 12 months of age (mean age = 7 months, mean angle of esotropia = 43 PD) and assessed at a mean of 24 months post-operatively, 41% (11 of 27) were aligned with a single injection; of subjects who were injected after 12 months of age (mean age = 25 months, mean angle of esotropia = 33 PD), 63% (19 of 30) were aligned with a single injection. A later prospective study by McNeer et al.[13] looked at children with IET in the range of 10 to 60 PD who were injected with 2.5 units of BTX-A between 4 to 48 months of age (mean angle of esotropia = 33 PD) and found that in long term follow-up (range = 1 to 7 years), 49% of subjects (37 of 76) had their deviations corrected to within $\pm$10 PD by a single BTX-A injection. One recent non-randomized prospective study compared BTX-A vs. conventional surgery in children with small to moderate angle esotropia with onset before 12 months of age.[19] Final outcomes were assessed at an average of 20 months following injection. For children with esotropia 30 prism diopters (PD) or less, good postoperative alignment was achieved in 34% of children treated with a single bilateral injection of 5.0 units of BTX-A vs. 60% of children treated with conventional surgery. Results were similar for children with esotropia larger than 30 PD (treated with 5.0 units of BTX-A for angles 35 to <50 PD and 7.5 units for angles >50 PD), with a 36% success rate by single injection of BTX-A vs. 69% success rate by BMR.[19] Another report of the success rate of BTX-A in moderate angle esotropia comes from a retrospective study assessing 60 children with infantile esotropia in the range of 30-50 PD (mean = 35 PD) who were injected with 2.5 to 3.0 units of BTX-A at an average of 6.5 months

of age.[15] Long-term follow-up of 2 to 9 years (mean 5.2 years) in these children showed that 88% were aligned within ±10 PD.[15] Nevertheless, all of these studies' results should be interpreted with caution because none were designed specifically to evaluate the effect of a single injection of BTX-A, one was retrospective, and all were non-randomized, conducted at only one or two centers, and/or had outcomes assessed in unmasked fashion.[10, 13, 19] For children with acquired esotropia, the only data on BTX-A outcomes is from one prospective study by Tejedor and Rodriguez.[16] Among 68 children with acquired esotropia (mean angle of esotropia = 35 PD) who were injected at doses of 1.25 to 5 units depending on the angle size, between 8 to 64 months of age (mean age = 36 months), long-term results (mean of 4.8 years of follow-up), showed 53% (36/68) were aligned with a single BTX injection.

1.2 Study Objective and Specific Aims

In the future, PEDIG plans to conduct a randomized clinical trial (RCT) to compare BTX-A with bilateral medial rectus muscle recession (BMR) as treatments for esotropia. There are concerns that recruitment for such a trial might not be feasible. Therefore a standard care data collection study is being conducted to collect data to evaluate recruitment potential for a randomized trial and to assist in defining certain aspects of the RCT protocol.

The primary objectives are:

- To determine how often PEDIG investigators are using BTX-A injection for treatment of esotropia, information which will be used to assess recruitment potential for the randomized trial.
- To describe what types of esotropia patients are being treated with BTX-A injection, information which will be used to refine the eligibility criteria for the randomized trial.

The secondary, exploratory objectives are to obtain preliminary data on surgical and post-surgical complications of BTX-A and on post-operative alignment and stereoacuity outcomes.

The study will enroll for up to a maximum of one year or 100 patients.

1.3 Synopsis of Study Protocol

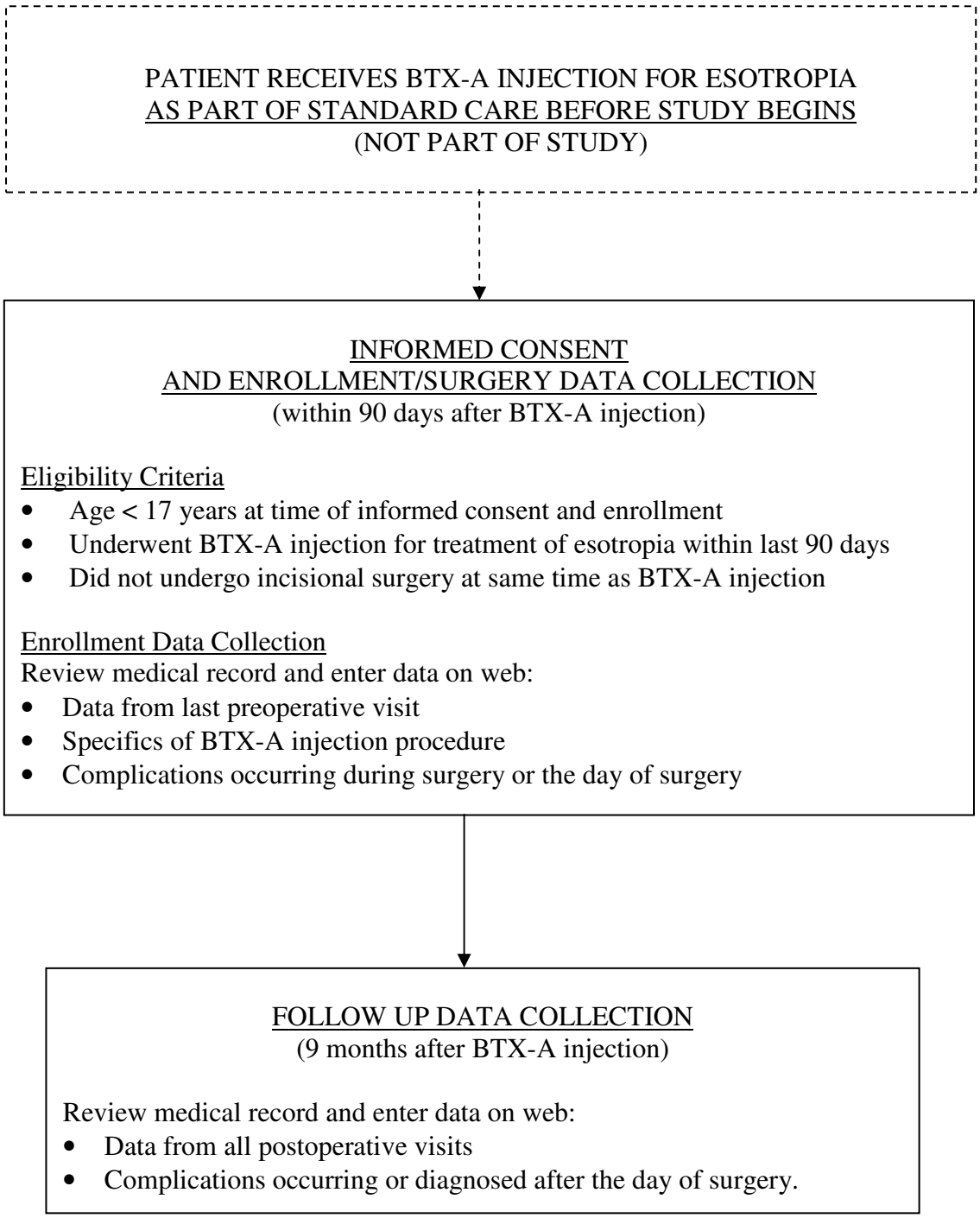
The protocol involves collecting data on children <17 years old at the time of informed consent and enrollment who have undergone BTX-A injection within the last 90 days as part of standard care treatment of esotropia. Informed consent and enrollment occurs after BTX-A injection has been performed; the surgical procedure is not part of the protocol. There is no protocol regarding post-operative or subsequent patient management and no procedures or visits will be performed specifically for the study. A central web-based electronic database will capture clinical data that is collected as part of usual care.

1.4 General Considerations

The study is being conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki and with the standards of Good Clinical Practice.

All participating centers will be established Pediatric Eye Disease Investigator Group (PEDIG) sites.

1.5 Flow Chart



2.0 Study Protocol

2.1 Eligibility Criteria

Children <17 years old at the time of informed consent and enrollment who have had BTX-A injection performed within the last 90 days as part of standard care treatment for esotropia of any type and magnitude are eligible.

Children who have had previous strabismus surgery or a prior BTX-A injection are eligible.

Children who underwent incisional surgery at the same time as BTX-A injection are not eligible.

2.2 Participant Enrollment and Data Collection

2.2.1 Informed Consent

Parents of children who have already undergone BTX-A injection performed as part of standard care for treatment of esotropia within the last 90 days and who agree to participate in the study will provide consent according to IRB requirements, before any personal health information is transmitted to the study database. Subject assent will be obtained according to IRB requirements when applicable.

Children who undergo BTX-A injection but are not participating in the data collection (either because their parents do not agree to participate or because informed consent was not attempted) will be logged in a de-identified manner on a non-enrollment log which will be transmitted to the Coordinating Center. No personal health information (PHI) will be transmitted for children who are not participating in the data collection and have not had informed consent signed.

2.2.2 Data Collection

The study data will consist of information collected during normal patient care, obtained from the clinic's medical record and parent. There is no testing or visits required for study participation. Data will be entered on the PEDIG website after enrollment and again 9 months after the BTX-A injection.

Data to be collected will include:

- Demographic information
- Medical history information
- Pre-operative examination findings
- BTX-A injection procedure and complications
- Post-operative complications
- Post-operative examination findings
- Additional treatment

3.0 Miscellaneous Considerations

3.1 Adverse Events

Adverse events will not be collected per se as the study is a data collection without a study protocol to be followed. However, complications of the BTX-A injection will be recorded on the data collection forms.

3.2 Benefits for Participants

There are no direct benefits for the participants. Results of this study will help determine the feasibility of a randomized trial comparing BTX-A to incisional surgery.

3.3 Risks

The risk to the subject for participation in the data collection is the unlikely chance that sensitive personal health information is viewed by an unauthorized person. Efforts are being made to ensure that this does not occur, as described in section 3.4.

3.3 Participant/Parent Reimbursement

No participant/parent reimbursement will be provided. There are no office visits or special testing for this study as any office visits and testing are part of usual medical care. Any costs will be the participant's/parent's responsibility just as they would be if they were not taking part in the study.

3.4 Confidentiality

Each participant will be assigned an identification number. All data and other information sent to the Jaeb Center for Health Research in Tampa, FL, which serves as the coordinating center for the project, will be identified with this number.

In addition, to help identify the study subject, the informed consent form and the assent form (if applicable) will include permission for the PEDIG Coordinating Center to receive the child's initials (first, middle, and last name initial).

Data will be entered on the Coordinating Center's secure website through an SSL encrypted connection. The Coordinating Center websites are maintained on Unix and Linux servers running Apache web server software and on a Windows server running IIS, all with strong encryption. The study website is password-protected and restricted to users who have been authorized by the Coordinating Center to gain access. No identifiable health information of an enrolled participant will be released by the Coordinating Center.

3.4.1 Website Data Transmission

All external requests for access to Jaeb websites are received by a dedicated Checkpoint firewall. The firewall server is used for no other purpose than network security; it stores no study data or other study materials. The Jaeb domain has been sub-netted into groups of IP addresses, which isolate company computers by assigning them IP addresses from a group not directly accessible by external systems. The firewall is configured to allow specific actions depending on the type of connection being requested. All inbound connection requests (HTTP, HTTPs, SMTP, etc.) are diverted to IP addresses in a separate network ("DMZ") that is isolated from other internal computers. All Jaeb private study websites are maintained on Linux and Windows servers running Apache and IIS web server software. When an HTTPS web connection request is received, the web server uses SSL (Secure Sockets Layer) technology to establish a secure connection with the user's computer and a private key is then used to encrypt transmitted data. Public sites with no need for encrypted connections (i.e., no study or patient data) are maintained on Windows and Linux web servers running Apache and IIS web server software. The private website will be password-protected and restricted to users who have been authorized by the CC to gain access. The site employs a multi-level authorization structure where certain areas are available to all authorized users and other areas available only to specified users. Within each area there are different levels of

authorization related to whether an individual has 'view only' privileges or has 'data entry' privileges; For instance, at a clinic, the investigators might be able to view certain data and generate reports, but a coordinator and backup coordinator would be the only clinic personnel authorized to enter and edit data. Regardless of view only versus data entry permissions, clinic staff only have access to certain patient information from their own clinic and cannot retrieve the data of the other clinics. The study chairperson and NIH program officers responsible for the project might be given 'view only' privileges for the entire website.

3.4.2 Data Maintained at the Jaeb Center

Patient data is stored in a secure SQL-server database. Access to the database requires necessary permissions, which give users different levels of access to the system. The CC is not provided with contact information as part of the study protocol. Patient data are identified by a unique ID number only and patient initials.

4.0 Statistical Considerations

The primary study objectives are to determine how often investigators are using BTX-A injection for treatment of esotropia and to describe the types of esotropia patients that are being treated with BTX-A injection, both of which will provide valuable information for planning a future randomized trial of BTX-A vs. traditional incisional surgery.

The secondary, exploratory objectives are to obtain preliminary data on surgical and post-surgical complications of BTX-A and on post-operative alignment and stereoacuity outcomes.

The study does not have a formal sample size as there are no formal scientific objectives or statistical analyses.

4.1 Dissemination of Study Results

Data and analyses may be disseminated in scholarly publications and presentations as well as publicly accessible websites. No identifying information from participants will be provided in the dissemination of results.

A de-identified dataset will be publically available after completion of the data collection, in accordance with NIH policy.

5.0 References

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