Management of Essential Infantile Esotropia With Botulinum Toxin A: Review and Recommendations

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INTRODUCTION

Much of the data published on botulinum toxin type A (BTA) in the treatment of strabismus have been derived from retrospective or empirical studies of general strabismus populations and do not singularly evaluate a specific strabismus type, such as infantile esotropia. Further, broad reviews of BTA therapy used to treat strabismus already have been published,¹,² which renders another review of lesser interest when compared to focusing on a specific strabismus type such as infantile esotropia. Virtually all published investigations on the use of BTA in the treatment of infantile esotropia, where many patients are studied and the author's data are used for analysis, yield favorable outcome results. However, negative opinions also have been presented in the literature. For example, Kushner,⁵ without furnishing data from his own experience in treating infantile esotropia with BTA injections, compared BTA to surgery in an editorial comment and considered surgery the superior method. Biglan et al⁶ considered BTA in infantile esotropia ineffective. Ing⁷ reviewed data on 12 patients and determined that BTA was less effective than surgery. Unfortunately, the foregoing negative opinions neglect to cite European or South American literature where the largest patient populations have been studied, the first by Campos³ in 1991. Thus, this article reviews the literature on BTA for infantile esotropia from published data where large patient populations are represented and evaluated.

EDUCATIONAL OBJECTIVES

1. To identify that bilateral medial rectus muscle Botulinum toxin A, as a treatment method for infantile esotropia, is efficacious, resulting in stable, permanent, binocular alignment.

2. To demonstrate that very early treatment for infantile esotropia can be achieved with low-dose simultaneous bimedial botulinum toxin injection.

3. To show that published outcomes from many authors, frequently from outside the United States, strongly support the foregoing conclusions.

See quiz on page 101; no payment required.

REVIEW

The first available analysis from a large database classified according to strabismus type was published in 1989.¹ The report included results from BTA injection in a group of patients with infantile
esotropia, but the data were derived from varying doses and a mixture of bilateral and unilateral med-ial rectus muscle injections in infantile esotropia, and the analysis was limited to complications and changes in the basic deviation following injection. McNeer et al. reported data derived solely from simultaneous bilateral medial 2.5-unit injections and examined the entire spectrum of anomalies commonly associated with infantile esotropia. A subsequent more inclusive study by McNeer et al. used a larger database created by adding new patients to the original study with a longer postinjection follow-up period. Investigations by other authors followed, but as previously noted, were published primarily in journals outside the United States. Conclusions from these contemporary studies generally agree that BTA is an efficacious therapeutic regimen in infantile esotropia.

A review of the European and South American literature is most revealing. Most investigations of BTA in infantile esotropia have been published in Spanish journals. Gomez de Llano et al. presented data from an extensive series of investigations beginning in 1991. The initial study on 41 patients documented bilateral medial BTA as the preferred therapeutic mode in infantile esotropia with a success rate (orthophoria ±10 PD) over a 9-month follow-up period was 70.2%. Their findings are similar to ours, specifically in regard to better results achieved in young esotropia patients with bilateral medial injections and producing large initial overcorrections. They further reported fewer secondary vertical deviations, or "alphabet," syndromes (A-, V-patterns). The doses used in these studies (eg, bilateral medial injections of 5 U BTA) are larger than ours, but this may be a reflection of the strength of BTA available in Spain.

Two years later, Gomez de Llano et al. reported results from 104 bilateral medial injections in patients with "convergent strabismus" ranging in age from 5-60 years with a success rate of 66.36%. Although the data undoubtedly contained some patients with infantile esotropia, strabismus classifications and numbers in that paper are difficult to evaluate. However, the authors' observations on the significance of initial or transient overcorrection and postinjection refractive errors are similar to ours.

In another series of 147 patients, Gomez de Llano et al. reported a success rate of 69.44%, again leading to the conclusion that simultaneous bilateral medial injections coupled with large initial overcorrections, identified as "greater paralysis," yielded the best results. In 1994, Gomez de Llano et al. reported a success rate of 78% from bilateral medial BTA injections in 52 patients with infantile esotropia. After separating preinjection esotropic angles of 40 PD or more, their success rate was 100%, stating: "This technique produces a greater correction of deviation when the pre-injection deviation is bigger. . ."

Finally, in 1996, Gomez de Llano et al. compared outcomes of 152 surgically treated and 440 BTA-treated esotropic patients and noted similar success rates of 74.32% and 76.04%, respectively. These figures, however, were not representative of a pure infantile esotropia population and were not all injected at an early age. The mean injection rate was 1.44±0.50 at an age of 5.82±5.96 years, and the surgical encounter was 1.27±0.52 times at an age of 8.18±10.7 years. A low incidence of secondary vertical anomalies also was noted. Nonetheless, this study stressed that a younger age and lesser deviation were significant factors in yielding a better outcome. These findings are supported further by a recent study of Hauviller and Gamio, who used bilateral medial BTA injections of 2.5-5 U in 20 patients between 7 and 24 months old with an initial mean esodeviation of 37.8 PD (25-55 PD). In this study, orthophoria was achieved in 70% of the patients.

Generally, the results of Gomez de Llano and colleagues are from larger patient databases than ours, but compare favorably to our outcomes regarding the success of motor alignment. These authors have stressed the lower incidence of secondary vertical anomalies requiring further treatment following BTA injection. They also have found a significant difference in the motor outcome of younger (<12 months) and older patients with infantile esotropia. Our studies, however, have not revealed a motor outcome difference between infants treated initially at <12 months of age and children treated at 24 months of age. Finally, the findings of Gomez de Llano and colleagues did not show postinjection accommodative esotropia developing late in all published studies or the very low incidence of latent or manifest latent nystagmus, as we have reported.

In France, Robert et al. evaluated bilateral
medial 2.5 unit BTA injections in eight patients with infantile esotropia, all treated after age 3 years. They obtained “lasting orthotropia” in four patients, a permanent angle reduction in two patients, and failure to respond permanently in the remainder because of ambylophia.

In Italy, Schiavi et al. published data following 2- to 2.5-unit bilateral medial BTA injection in 25 esotropic patients <8 months. The minimum postinjection observation period was 1 year. They reported a mean reduction of 40 PD in 10 essential patients with infantile esotropia and a mean reduction of 38 PD in “esotropia normosensoriale tardiva di Lang.” Botulinum toxin A injection was used successfully in the remaining 5 patients to augment ambylophia therapy by eliminating the adduction bias of the ambylopic eye while patching the better eye. This latter point has been overlooked in the American literature, but it is nonetheless a valid contribution.

In a 1993 editorial review, Campos reported orthotropia or cosmetically acceptable small angle esotropia after 2 years following bilateral medial BTA injection in 20 patients. In 1996, Campos reported on 51 patients with infantile esotropia treated with bilateral medial injections before the age of 8 months, indicating that a single injection of 2.5-3 units of BTA eliminated the need for surgery in 87.6% of the cases. He also stated that in his experience, infantile esotropia treated after the age of 8 months had not provided “stable” results. Campos’ technique differs from ours in that he makes a conjunctival incision using inhalational anesthesia to expose the muscle for direct viewing. In general, our conclusions agree with those of Campos, but we fail to see the need for an incision to expose the muscle. First, in most cases, the electromyogram (EMG) signal is very reliable. Second, if that technique fails, it is easy to see the muscle and tendon with minimum magnification under the operating room lights. Third, the needle only needs to enter the distal anterior portion of the medial rectus muscle for the toxin to be effective. The long, or global, fibers, act as a wick, allowing the toxin to spread to the posterior or shorter orbital fibers where BTA exerts the major action seen clinically as transient paresis. The global fibers are affected secondarily. Finally, the surgeon has a unique advantage using BTA because the major risk of mildly misplaced toxin is the failure to produce the intended muscle paresis. Moreover, there is virtually no risk of permanent pathologic damage to the extraocular muscle. Nonetheless, with this in mind, we strongly advise against probing the EMG needle-electrode posteriorly in the orbit. This usually happens because a good EMG signal is not obtained and one goes searching for it farther back. However, this maneuver markedly increases the risk of leakage to adjacent muscles and the probability of globe penetration.

Our experience, supported by data from studies outside the United States, has allowed us to set forth a management strategy for infantile esotropia. At the onset, it is important to see the infant as soon as esotropia is suspected. One of the reasons lies with the potential for cure of an intermittent or manifest deviation with alternating patching alone. Equally important is that alternate patching should be instituted early to restore or preserve binocular vision. Using motion symmetry visually evoked responses, we have found the open window for developing binocular vision in infants with esotropia ends at approximately 8 months. Alternate patching prior to 8 months yields the best potential for binocular vision. Because BTA injection has minimal risk, it can be used early and repetitively without the need for intubation or general anesthesia. We have used BTA as early as age 4 months without experiencing significant problems, although younger patients with smaller angle deviations may require more injections than older patients with larger deviations. However, the patients who benefit the most from this approach are those with small angle (<15 PD) esotropia, who otherwise would not have been managed with surgery and consequently would have a poor prognosis for the development of normal binocular vision and stereopsis, particularly if they are younger than 12-18 months of age. Moreover, if BTA injection is selected by the physician, it is best used as the primary therapeutic mode. Although recent findings by Tejedor and Rodriguez have demonstrated good results using BTA as a follow-up to surgery, we have found BTA less effective following surgical procedures for infantile esotropia (especially in correcting consecutive exotropia), probably because the length/tension properties of the extraocular muscles have been sufficiently altered to interfere with the necessary motor adaptation.

In our study of BTA-treated infantile esotropia,
patients developed secondary vertical anomalies, but the incidence generally was less than that found in surgically treated infantile esostrpia. In addition, treatment of secondary vertical strabismus, with either BTA or surgery, was necessary in a comparatively smaller number of cases because the degree of vertical deviation was frequently below the usual indication for correction. Dissociated vertical deviation was found in 14%, and 3% required surgery. The incidence of overacting inferior oblique muscles (invariably bilateral) after injection was 29%, but only 5% required surgery. Because the incidence of secondary vertical anomalies was relatively small and because our experience showed unpredictable response with inferior oblique BTA injection, we opt for surgery (myectomy) as a management strategy for overacting inferior obliques. Similarly, given the low surgically indicated incidence and because the risk of temporary ptosis following superior rectus muscle BTA injection is rather usual, we choose surgery (superior rectus muscle recession) when encountering dissociated vertical deviation.

One of the most significant problems in the early management strategy of infantile esostrpia is that hyperopic refractive errors typically develop around 19 months age, which changes the disorder diagnosis from infantile esostrpia to accommodative esostrpia, requiring lens correction rather than repeated BTA injection or surgery for correction. This apparently happens despite being unable to demonstrate a substantial refractive error at an earlier age. This phenomenon is not unique to BTA-treated patients, as it appears all too frequently in reports of surgically treated infantile esostrpia populations.

There does not appear to be a satisfactory method for predicting which patients with infantile esostrpia will develop hyperopic refractive errors. However, our data indicate that girls have a significantly higher probability of developing refractive errors than boys at the same age of treatment. Serial refractions, particularly around 19 months of age, provide the best sentinel, but we are yet unable to alter the development or the progression of strabismic hyperopia that may follow early correction of the strabismic deviation. One clinical clue that is helpful early in the management program is the common sign of variation or “wobbly angle” of the strabismic deviation, even in the absence of demonstrable cycloplegic hyperopia.

RECOMMENDATIONS

We recommend the following protocol for managing infantile esostrpia with BTA injection:
1. Early examination, preferably as soon as any esostrpia is observed by a parent, pediatrician, or family practitioner.
2. Motion symmetry visually evoked response monitoring of binocular vision, if available, or monocular testing of optokinetic nystagmus symmetry (nasal-to-temporal and temporal-to-nasal).
3. Alternate patching for a minimum of 2 weeks prior to BTA injection, especially in infants.
4. Bilateral medial 2.5-U BTA for persisting esostrpic deviations ≥10 PD.
5. Temporary lens, patching, or Fresnel prism therapy for small angle residual deviations following injection.
6. Repeat bilateral medial 2.5-U injection after response failure, even for small angle deviations (<10 PD) and as soon as 1 month following the initial injection.
7. Constant monitoring by cover test and refraction, particularly around age 19 months as this is the usual onset age of significant hyperopia found in our study (the treatment then becomes maximum hyperopic correction rather than additional injection or surgery).
8. Prescribing hyperopic correction over +2.00 diopters as soon as it becomes manifest.
9. Inferior oblique overaction and dissociated vertical deviation may be more predictably responsive to usual surgical techniques than BTA injection.

CONCLUSION

It is conceivable that continued evaluation of these children as they mature into adults will reveal unanticipated problems, such as late consecutive esostrpia, but with most patients followed ≥5 years, the incidence is very low. It is also possible that we may modify our management strategy to account for new discoveries; therefore, we continue to follow these patients where cooperation permits. Currently, we are evaluating late-onset latent, manifest-latent nystagmus, or both with electronystagmography and video recordings. So far, however, we have no reason to alter our observation that bilater-
al medial 2.5-U injection is anything other than a safe, efficacious alternate to surgery for infantile esotropia. Finally, we agree with Birch et al \(^4\) who observed that one of the most important factors in treating infantile esotropia is keeping the eyes aligned as much as possible during the visual development period. Bilateral medial rectus muscle botulinum toxin injection furnishes a reliable, safe, easily administered therapeutic regimen to accomplish this goal with any frequency at any age.

**REFERENCES**