The resurgence of botulinum toxin injection for strabismus in children

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Purpose of review
The present review discusses recent advances in the use of botulinum toxin for the management of strabismus in children.

Recent findings
Botulinum toxin injection produces similar results compared to surgery for certain subtypes of strabismus, especially acute onset esotropia. It may be more effective in many subtypes of esotropia where surgery has been less reliable, including partially accommodative esotropia, esotropia associated with cerebral palsy, and thyroid eye disease.

Summary
Small retrospective studies have demonstrated the efficacy of botulinum toxin in the treatment of many types of pediatric strabismus, providing some guidance for clinicians to determine which patients would benefit most from this intervention. Although administration of botulinum toxin is generally accepted as a reasonable option in select cases, many strabismus surgeons have not fully embraced the treatment, in part because of perceived disadvantages compared to surgery and difficulty in identifying subsets with the highest potential for therapeutic success. A recent study compared the administration of botulinum toxin in children with acute-onset esotropia to surgical correction and found botulinum toxin had a statistically equal success rate, but with the advantage of significantly less time under general anesthesia. In addition, botulinum toxin has been recently tried in patients with partially accommodative esotropia, esotropia associated with cerebral palsy, cyclic esotropia, and in patients with thyroid eye disease. The present review will discuss current clinical recommendations based on recent studies on the use of botulinum toxin in children with strabismus.

Keywords
acute onset esotropia, botulinum toxin, complications, strabismus

INTRODUCTION

Since its initial evaluation as a treatment for strabismus in pediatric patients, botulinum toxin has emerged as an alternative to surgery for a variety of strabismus subtypes, including small-to-moderate angle infantile esotropia, acute-onset esotropia, residual esotropia, consecutive exotropia, and acute sixth nerve palsy. There are many potential advantages of botulinum injection over standard strabismus surgery. Administration of botulinum toxin is a substantially shorter procedure that may reduce general anesthesia exposure. It also causes minimal scarring of the extraocular muscles and surrounding tissues compared to surgery. The minimally invasive nature of the injections also confers a theoretically lower risk of endophthalmitis and other serious side effects seen with strabismus surgery. Many studies have revealed improvement in binocularity following the use of botulinum toxin [1].

However, widespread adoption of botulinum toxin in strabismus management has been limited by its perceived disadvantages. The muscle response to botulinum toxin injection is more variable than in strabismus surgery, and there are currently no standardized botulinum toxin dose recommendations based on angle of deviation, in contrast to the standardized tables available for strabismus surgery. There is a high recurrence rate of the strabismus after botulinum toxin injection, necessitating subsequent injections [2▪,3]. The toxin also

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Curr Opin Ophthalmol 2017, 28:460–464
DOI:10.1097/ICU.0000000000000408

KEY POINTS

- Botulinum toxin injection is as effective as surgery in acute onset esotropia.
- Botulinum toxin injection for strabismus reduces anesthesia and recovery time.
- Botulinum toxin should be considered an alternative in many subtypes of esotropia.

frequently spreads to surrounding muscles, resulting in transient vertical deviation and ptosis.

Recently, there has been renewed interest in the use of botulinum toxin injection in strabismus treatment. Wan *et al.* [4▪▪], recently reported botulinum toxin injection achieved statistically similar success rates compared to surgery in children with acute-onset esotropia, with the advantage of markedly shorter anesthesia time. Several other recent papers have shown favorable success rates with botulinum toxin for other types of strabismus. The present review will outline the general advantages and disadvantages of botulinum toxin injection, and which subtypes of strabismus appear to be most responsive to treatment with botulinum toxin.

ADVANTAGES OF BOTULINUM TOXIN INJECTION OVER SURGERY

Anesthesia time

One of the greatest benefits of treatment with botulinum toxin is the short duration of the procedure and consequently reduced amount of time requiring general anesthesia. In a recent retrospective study [4▪▪] comparing surgery and botulinum toxin injection for acute-onset strabismus, children receiving botulinum toxin injection averaged only 5 min of general anesthesia, compared to an average of 71 min for the surgery group. Anesthesia is generally administered via mask only for botulinum toxin injection. With the recent FDA warning that prolonged anesthesia for children younger than the 3 years of age may affect brain development, limiting the time under anesthesia has become a higher priority [5]. In addition to a significant reduction in time under anesthesia, botulinum toxin administration also significantly reduces time spent in the postanesthesia care unit [4▪▪].

Reduced risk of overcorrections

Multiple studies have reported that overcorrections with botulinum toxin injections are rare once the toxin has worn off [4▪▪,6–9,10▪], which usually occurs within 3–6 months following injection. This gives peace of mind to both the surgeon and the parents of the child, as overcorrections of esotropia in particular can lead to multiple future surgeries. This is an especially favorable option in cases of partially accommodative esotropia, esotropia associated with developmental motor delays such as cerebral palsy, and esotropia undercorrected after surgery, when the risk of consecutive exotropia following surgery is increased [7,10▪,11,12]. However, one study [12] found that there were still a 13.7% occurrence of overcorrection with the use of botulinum toxin in adults with cerebral palsy.

Muscle preservation

Botulinum toxin administration preserves muscle tissue and appears to cause minimal scarring of conjunctiva or Tenon's, thus reducing surgical time if future surgery is needed. This is particularly advantageous in cases where high rates of reoperation are expected, such as infantile esotropia [3,6] and esotropia associated with cerebral palsy [12]. However, repeated injections of botulinum toxin have been associated with muscle atrophy, and the exact mechanism and histopathological changes after botulinum toxin injection have still not been fully determined [13▪].

Earlier treatment

Another important advantage is that many surgeons feel more comfortable with earlier treatment of strabismus with botulinum toxin than with surgery. Earlier treatment can lead to an earlier re-establishment of binocular vision, potentially lowering the risk of amblyopia and reduced stereopsis [8]. Wan *et al.* [4▪▪] reported a median time to treatment from the onset of strabismus of 3 months for patients treated with botulinum toxin, whereas patients in the surgical group were treated an average of 6.8 months after onset.

Relatively painless postoperative period

Furthermore, patients should experience little to no pain following injections, in contrast to the postoperative pain and discomfort patients usually experience following standard strabismus surgery. The expectation of a relatively painless postoperative period may help ease anxiety in both patients and their parents [14].

Less invasive procedure

Although serious complications are rare in standard strabismus surgery, botulinum toxin injection

should theoretically reduce the incidence further. As there is no conjunctival incision required, suture granulomas have not been reported following botulinum toxin injections [4▪▪]. In theory by eliminating scleral sutures, the incidence of the rare but devastating complication of endophthalmitis should also be reduced. With botulinum injections, there is still a possibility of globe perforation. One recent study reported cases of unilateral tonic pupil observed following bilateral botulinum toxin injection [15▪]. It was suggested that technical difficulty of the injection may account for this side effect, as all cases presented on the same side following injection by the same surgeon.

DISADVANTAGES OF BOTULINUM TOXIN INJECTION COMPARED TO SURGERY

Lower success rate overall compared to surgery

Overall success rates of botulinum toxin in all types of strabismus have been reported as lower compared to surgery [2▪]. A retrospective cross-sectional study found that botulinum toxin injection alone was a significant predictor of both reoperation and abnormal postoperative binocularity compared to fixed-suture surgery in the treatment of all types of horizontal strabismus [2▪]. It should be noted that this analysis was performed by comparing the outcomes of 7521 patients who underwent fixed-suture surgery, and only 49 who were treated with Botulinum toxin, which included patients with esotropia, exotropia, or Duane syndrome, with a paralytic cause identified in 10 cases. The aggregated data showing lower success rates of botulinum toxin treatment for all types of strabismus has likely contributed to the false perception that botulinum toxin is inferior to surgery in all cases. It is important that such data not be interpreted as evidence against the efficacy of botulinum toxin as subanalysis of specific types of strabismus was not completed, highlighting the importance of identifying strabismus subtypes with the highest potential for successful outcomes.

Less precision and reduced efficacy in large angle strabismus

The procedure itself is not as precise, and there are no specific botulinum toxin dose recommendations based on angle of deviation, in contrast to the standardized tables available for strabismus surgery. It has been reported that treatment with botulinum toxin is not as effective in patients lacking binocular vision potential [1] or in patients with large-angle infantile esotropia [3]. The evidence demonstrating preliminary angle of deviation as a predictor of successful outcome is not consistent [6], and more data are needed to effectively guide clinical decision-making for specific subsets.

Transient postoperative exotropia and ptosis

Other potential drawbacks include a longer duration of postoperative overcorrections and high incidence of transient ptosis and vertical deviations [1]. Wan *et al.* [4▪▪] reported a postoperative ptosis rate of 50% with full resolution after a median of 6 weeks, including one case of transient pupil occlusion that did not result in amblyopia. They reported a postoperative exotropia rate of 56%, with all cases resolving after a median of 8 weeks. A retrospective review of five patients with persistent esotropia treated with a single injection of botulinum toxin reported one case of hypertropia in the treated eye, which later developed dissociated vertical deviation and amblyopia [7]. Although no other reports of postbotulinum toxin amblyopia development were identified, it is important to closely monitor young patients at risk for occlusive amblyopia. Although these effects are expected to resolve within a few months, the visible appearance of ptosis may cause parents considerable distress, and they will likely need continued reassurance that this effect is neither harmful nor permanent.

Various techniques are used in an attempt to minimize the fairly high incidence of postoperative ptosis. It has been suggested that a more concentrated solution, precise needle positioning, and elevation of the head immediately after injection may reduce incidence of ptosis [4▪▪]. In addition, identification of the lowest effective dose of botulinum toxin may reduce the incidence of postoperative ptosis and vertical deviation, as it appears to be associated with higher doses [16].

Used almost exclusively to weaken the action of the medial rectus muscles

Although surgery can be performed on all six extraocular muscles, and is used to both strengthen and weaken the action of the muscles, botulinum toxin injection has been used almost exclusively as a weakening procedure of the medial rectus muscles. Injection of the anesthetic bupivacaine has been shown to correct horizontal strabismus by enhancing muscle action. It has been suggested that the anesthetic induces myofibril damage, which triggers a regenerative response resulting in gradual adaptive changes in muscle length and increased force [17,18]. For large angles of deviation treated with

bupivacaine, botulinum toxin injection into antagonist muscles has been shown to improve alignment, likely by enabling the agonist to undergo remodeling at a reduced length [17]. After an average of 1.9 treatments, this combination treatment achieved an absolute correction of 20.9 PD in patients with an initial deviation greater than 25 PD.

SUBSETS OF STRABISMUS MOST LIKELY TO BENEFIT FROM BOTULINUM TOXIN INJECTION

Acute-onset comitant esotropia

Wan *et al.* [4▪▪] recently published the first study comparing botulinum toxin and standard strabismus surgery as a primary treatment for acute comitant esotropia. This retrospective study compared results from 16 patients who received a single dose of botulinum toxin injected into both medial rectus muscles to 33 patients who received bilateral medial rectus muscle recessions. All patients were within 2–10 years of age and presented within 6 months of onset of strabismus. The median initial deviation in both groups was 35 PD, and patients were examined 6 and 18 months after intervention. Of the 16 patients who received botulinum toxin injection, 14 received 5 units, one patient received 4 units, and one received 3.5 units. At 6-month follow-up, successful outcome was reported in 13 (81%) patients in the chemodenervation group, defined as a deviation of 10 prism diopters or less with evidence of binocular single vision and no need for retreatment. Of the surgery group, 20 out of the 33 patients were successful (61%), which was not statistically different from the chemodenervation group. The children undergoing botulinum toxin injection had the advantage of significantly less time under general anesthesia (5 vs. 71 min) and shorter time in the recovery room. Compared to the surgery group, patients receiving the botulinum toxin injections were treated on average 3 months earlier after onset of strabismus, which may be partially due to the fact that botulinum toxin can be administered regardless of angle stability or concern for overcorrection, which may delay surgery. Although the chemodenervation group had the disadvantage of a high incidence of transient ptosis and exotropia, the advantages of botulinum toxin injection over surgery make it a favorable alternative for the treatment of acute-onset comitant esotropia.

In subsets of esotropia with greater risk of overcorrection with surgery

Botulinum toxin should be considered in the treatment in conditions with high rates of surgical overcorrection, such as partially accommodative esotropia [10▪] and esotropia associated with cerebral palsy [19], due to concerns of permanent overcorrection following surgery. It has also been successfully used to reduce the need for subsequent surgeries in children with persistent esotropia [7], and in children with consecutive esotropia following surgical correction of intermittent exotropia [8].

Cyclic esotropia

A recent case report described the use of botulinum toxin to successfully treat a 3-year-old girl with 48-h cycle esotropia [20]. Although surgery has a high rate of success in this condition, a single dose of botulinum toxin can be used earlier and potentially eliminate the need for surgery.

Thyroid eye disease

Botulinum toxin has been used in adults to correct diplopia secondary to thyroid eye disease during the active inflammatory phase [21,22]. Treatment with botulinum toxin was able to reduce deviations and delay or even prevent surgery, especially in patients with esotropia, small angles of deviation, and low degrees of extorsion [21].

CONCLUSION

Botulinum toxin injection is a powerful tool and valuable addition to the expertise of strabismus surgeons. Its advantages over surgery include only a brief or local anesthesia requirement, little to no pain after injection, theoretically reduced risk of serious surgical complications such as endophthalmitis, low risk of overcorrections, and minimal scarring of the extraocular muscles. It has the disadvantages of a protracted time of misalignment and possible ptosis after injection, which can last up to 3 months, and a greater possibility of undercorrections in certain populations. Wan *et al.* [4▪▪] have shown that botulinum toxin injections have success rates comparable to surgery for acute onset esotropia. The corresponding author (J.M.E.) has also had a success rate similar to what Wan *et al.*, although with a shorter follow up time, with the use of botulinum toxin type A in acquired nonaccommodative esotropia in children. It should also be considered as an alternative to surgery in conditions where surgery is associated with a higher risk of overcorrections, such as partially accommodative esotropia and children with motor delays such as from cerebral palsy. Botulinum toxin chemodenervation appears to have a less promising treatment effect compared to standard strabismus surgery in

children with long-standing esotropia and in children with large angle esotropia.

Acknowledgements

We would like to thank Alejandra de Alba MD for sharing her extensive experience with botulinum toxin chemodenervation.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Rowe FJ, Noonan CP. Botulinum toxin for the treatment of strabismus. Cochrane Database Syst Rev 2017; 3:CD006499.
2. Leffler CT, Vaziri K, Schwartz SG, *et al.* Rates of reoperation and abnormal
■ binocularity following strabismus surgery in children. Am J Ophthalmol 2016; 162:159–166.e9.

A retrospective cross-sectional study found botulinum toxin injection alone for horizontal strabismus to be a significant predictor of both reoperation and abnormal postoperative binocularity compared to fixed-suture surgery, although this analysis grouped all types of horizontal strabismus together.

3. De Alba Campomanes AG, Binebaum G, Campomanes Eguiarte G. Comparison of botulinum toxin with surgery as primary treatment for infantile esotropia. J AAPOS 2010; 14:111–116.
4. Wan MJ, Mantagos IS, Shah AS, *et al.* Comparison of botulinum toxin with
■■ surgery for the treatment of acute-onset comitant esotropia in children. Am J Ophthalmol 2017; 176:33–39.

This study is the first comparative study demonstrating noninferiority of botulinum toxin compared to standard strabismus surgery in children with acute-onset comitant esotropia. Botulinum toxin injection significantly reduced the amount of time under general anesthesia as well as time spent in the postanesthesia care unit.

5. FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. U.S. Food and Drug Administration; 2016; https://www.fda.gov/Drugs/DrugSafety/ucm532356.htm. [Accessed 12 April 2017].
6. Gursoy H, Basmak H, Sahin A, *et al.* Long-term follow-up of bilateral botulinum toxin injections versus bilateral recessions of the medial rectus muscles for treatment of infantile esotropia. J AAPOS 2012; 16:269–273.
7. Lambert SR, Shainberg MJ. The efficacy of botulinum toxin treatment for children with a persistent esotropia following bilateral medial rectus recessions and lateral rectus resections. Am Orthopt J 2013; 63:24–28.
8. Couser NL, Lambert SR. Botulinum toxin a treatment of consecutive esotropia in children. Strabismus 2012; 20:158–161.
9. Dawson ELM, Marshman WE, Adams GGW. The role of botulinum toxin a in acute-onset esotropia. Ophthalmology 1999; 106:1727–1730.
10. Flores-Reyes EM, Castillo-Lopez MG, Toledo-Silva R, *et al.* Botulinum toxin
■ type A as treatment of partially accommodative esotropia. Arch Soc Esp Oftalmol 2016; 91:120–124.

Botulinum toxin injection was investigated as an accessible, lower-cost option for the treatment of partially accommodative esotropia, producing significant improvements in angle of deviation at 1-year follow-up. It was noted that consecutive exotropia 1 week after injection may be a predictor of therapeutic success.

11. Habot-Wilner Z, Spierer A, Glovinsky J, Wygnanski-Jaffe T. Bilateral medial rectus muscle recession: results in children with developmental delay compared with normally developed children. JAAPOS 2006; 10:150–154.
12. Ameri A, Mirmohammadsadeghi A, Makateb A, *et al.* Clinical outcomes of botulinum toxin injection in patients with cerebral palsy and esotropia. Strabismus 2015; 23:8–13.
13. Li J, Allende A, Martin F, Fraser CL. Histopathological changes of fibrosis in
■ human extra-ocular muscle caused by botulinum toxin A. J AAPOS 2016; 20:544–546.

This study reports three cases of botulinum-induced fibrosis and atrophy of human extraocular muscles.

14. Fortier MA, Kain ZN. Treating perioperative anxiety and pain in children: a tailored and innovative approach. Paediatr Anaesth 2015; 25:27–35.
15. Pediatric Eye Disease Investigator Group. Christiansen SP, Chandler DL, Lee
■ KA, *et al.* Tonic pupil after botulinum toxin-A injection for treatment of esotropia in children. J AAPOS 2016; 20:78–81.

A high rate of tonic pupil was reported following botulinum toxin, highlighting the importance of careful intramuscular needle placement and surgeon experience.

16. Sener EC, Sanac AS. Efficacy and complications of dose increments of botulinum toxin-A in the treatment of horizontal comitant strabismus. Eye (Lond) 2000; 14:873–878.
17. Miller JM, Scott AB, Danh KK, *et al.* Bupivacaine injection remodels extraocular muscles and corrects comitant strabismus. Ophthalmology 2013; 120:2733–2740.
18. Debert I, Miller JM, Danh KK, Scott AB. Pharmacologic injection treatment of comitant strabismus. J AAPOS 2016; 20:106–111; e2.
19. Petrushkin H, Oyewole K, Jain S. Botulinum toxin for the treatment of early-onset esotropia in children with cerebral palsy [letter]. J Pediatr Ophthalmol Strabismus 2012; 49:125.
20. Jones A, Jain S. Botulinum toxin: a novel treatment for pediatric cyclic esotropia. J AAPOS 2014; 18:614–615.
21. Akbari MR, Ameri A, Keshtkar Jaafari AR, Mirmohammadsadeghi A. Botulinum toxin injection for restrictive myopathy of thyroid-associated orbitopathy: success rate and predictive factors. J AAPOS 2016; 20:126–130.e1.
22. Granet DB, Hodgson N, Godfrey KJ, *et al.* Chemodenervation of extraocular muscles with botulinum toxin in thyroid eye disease. Graefes Arch Clin Exp Ophthalmol 2016; 254:999–1003.