

The Use of Botulinum Toxin to Treat Infantile Esotropia: A Systematic Review With Meta-Analysis

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PURPOSE. The purpose of this review was to examine the efficacy of botulinum toxin in the treatment of infantile esotropia and to evaluate the average response of BT and its complication rates.

METHODS. A research was performed in the Latin American and Caribbean Literature on Health Sciences (LILACS), MEDLINE, and Cochrane Central Register of Controlled Trial (CENTRAL). The database was searched between December 28, 2016 and January 30, 2017. The selection was restricted to articles published in English, Spanish, or Portuguese. There were no date restrictions in the search.

RESULTS. Nine studies were eligible for inclusion. The grouped success rate of BT treatment in infantile esotropia was 76% (95% confidence interval [CI]: 61%–89%). For the success rate, I^2 of 94.25% was observed, indicating a high heterogeneity ($P < 0.001$). The complication rates were also analyzed. The grouped consecutive exotropia (XT) rate was 1% (95% CI: 0%–2%). The grouped ptosis rate was 27% (95% CI: 21%–33%). The grouped vertical deviation rate was 12% (95% CI: 4%–22%). The mean change of the deviation after BT injection was -30.7 (95% CI: -37.7 , -23.8), demonstrating a significant improvement in alignment.

CONCLUSIONS. Botulinum toxin injection into medial recti muscles reveals to be a safe procedure and a valuable alternative to strabismus surgery in congenital esotropia, especially in moderate deviations.

Keywords: botulinum toxin, strabismus, infantile esotropia

Infantile or congenital esotropia is a large angle convergent deviation with onset prior to 6 months of age in neurologically normal children. It is usually not related to refractive errors and often associated with other motor abnormalities, such as inferior oblique overaction, dissociated vertical deviation (DVD), and latent nystagmus.^{1,2}

The prevalence of esotropia in the population is approximately 1%, while the prevalence of infantile esotropia reported at birth is 27 per 10,000 live births.¹ Children who develop infantile esotropia begin it at approximately 4 months of age. Its etiology is a source of controversy and remains unknown.^{1,3}

Most investigators agree that early surgical intervention improves both motor and sensory outcomes, even if early surgery reoperation is common and binocular outcomes can be poor.^{4,5} Although the treatment of choice for most patients remains surgical, opinions continue to differ as to the best approach, particularly in small and moderate angle deviations.

Alan Scott pioneered the pharmacologic treatment of strabismus in 1980.⁶ Botulinum toxin (BT), which is an exotoxin of the bacterium *Clostridium botulinum*, was approved by the FDA in 1990. Botulinum toxin A is a large protein molecule that, when injected in the muscle, remains at the nerve terminal, inhibiting the release of acetylcholine and resulting in muscle weakness or paralysis 3 to 5 days after the injection. An irreversible binding occurs and the muscle paralysis lasts approximately 8 to 12 weeks.³ The chemo-denervated muscle lengthens and its antagonist contracts.

Sensory mechanisms may also play a role in the realignment after treatment with BT A in some types of strabismus. The visual axes may adopt an alignment that permits binocular single vision; and this may persist or regress, demanding further treatment.^{3,6,7} Initial doses of botulinum toxin for individual muscles were initially suggested by Alan Scott (Table 1).⁸

Botulinum toxin injection in the extraocular muscles is an alternative option that has become well established in some cases of adult strabismus, such as sixth nerve palsy. Its use in children is more controversial, as it requires sedation and some complications, as ptosis, may be more frequent in this population.^{3,6,7} Nevertheless, many investigators have advocated the use of botulinum toxin as a good alternative in the treatment of infantile esotropia, as it is a less invasive procedure than muscle surgery.

The success of BT injections in infantile esotropia seems to be related to the age that the treatment is performed. There is a critical age when the medial rectus muscle is more sensitive to the chemodenervation induced by BT, allowing the antagonist lateral rectus to regain its function. Besides, morphologic modifications in the structure of the extraocular muscles (i.e., tight medial recti on the forced duction test) are apparently still deficient at early ages. It has been demonstrated that botulinum toxin affects the extraocular muscles in infant monkeys more severely and for longer than those in adult monkeys.^{9,10}



TABLE 1. Botulinum Toxin Dosage for Strabismus Treatment

	Adults >12 y	Children			
		>12.5 kg	10–12 kg	6–9 kg	<6 kg
Horizontal or vertical deviations <20 PD	1.25–2.5 U	1.25 U	1.25 U	1.25 U	-
Horizontal or vertical deviations 20–50 PD	2.5–5 U	1.25–2.5 U	1.25–1.75 U	1.25 U	1 U
Persistent sixth nerve palsy of ≥ 1 mo duration (medial rectus)	1.25–2.5 U	1.25 U	1.25 U	1.25 U	1 U

U, units.

It could be assumed that early treatment allows a “self-adjusting” sensorimotor mechanism to support stable binocular alignment near orthoposition, once the motor system has been suitably modified. In fact, at early ages, the central connections of the sensory and motor visual systems can still be changed.

The complications reported on the use of BT include secondary ptosis; initial consecutive exotropia (XT) lasting up to 2 to 3 months; and the temporary effect of the BT injection itself.^{8,13–18} Also, many studies show that multiple injections may be needed to sustain the alignment effect.¹⁹ On the other hand, the advantage is that BT is a simple treatment, in which injections are performed under minimal anesthesia without intubation. However, some studies show that the motor and sensory outcomes may be significantly worse than surgery even with multiple injections.²⁰

What is the importance of this review?

Currently there are no guidelines about the use of BT in the treatment of infantile esotropia. In the past decades, several retrospective case series have been published on its use to treat strabismus. The studies were performed in different types of strabismus, using different doses, methods and follow-up times. The outcomes were diverse.

The main purposes of this study were to examine the efficacy of BT in the treatment of infantile esotropia and to evaluate its dose response and complication rates.

METHODS

Search Methods for Identifying Studies

Research was performed in the Latin American and Caribbean Literature on Health Sciences (LILACS); MEDLINE; and Cochrane Central Register of Controlled Trial (CENTRAL). The database was searched between December 28, 2016, and January 30, 2017. The selection was restricted to articles published in English, Spanish, or Portuguese. There were no date restrictions in the search.

The strategies used were: botulin* toxin*; botulinum toxin; Clostridium botulin; Botox; strabismus; esotropia; infantile esotropia; congenital esotropia.

Study Selection

We screened the titles and abstracts from the search to determine if the study met the inclusion criteria.

We included trials in which BT of any brand was used and compared the results of the treatment of infantile esotropia.

Data Collection and Risk of Bias Assessment

We searched for the following elements from the studies:

1. Inclusion and exclusion criteria, presence of a group of patients with infantile esotropia, follow-up period, success criteria.

2. Age at which the procedure was performed, history of previous treatment.
3. Type of BT used, dose, and number of injections.
4. Motor and sensory outcomes after a minimum follow up of 6 months.
5. Effects.
6. Bias.

The following analyses were performed: success rate and possible factors associated to success; association of complications with the dose of BT and complications reported at each study; and mean variation of the deviation after BT injection.

A minimum follow-up of 6 months was required to access the primary outcomes. Motor success was defined as postprocedure deviation within 10 prism diopters (PD) of orthotropia. Sensory success was defined as normal ranges of binocular single vision.

The following adverse outcomes were considered: induced ptosis, induced vertical deviation, and consecutive exotropia.

Eligibility Criteria

The criteria for considering studies for this review were: studies analyzing neurologically normal patients with infantile esotropia, minimum follow up of 6 months, botulinum toxin injection performed in both medial recti muscles, and criteria of success postoperative deviation within 10 PD in primary position.

Exclusion Criteria

The criteria for excluding studies for this review were: previous strabismus surgery in the population studied; botulinum toxin injected in only one medial rectus muscle; population studied including types of esotropia other than infantile esotropia

Data Synthesis and Analysis

The heterogeneity between studies was evaluated through the use of the I^2 statistics.²¹ The I^2 statistics varies from 0 to 100, and the higher it is, the greater the heterogeneity observed among the rates.

The complications (consecutive exotropia, ptosis, and vertical deviations), and the deviation change were presented using a random model. Meta-regression models were fitted to identify possible sources of heterogeneity between the estimations.

A significance level of 5% was used for all statistical tests. Statistical analyzes were performed using statistical software (STATA 12.0; Stata Corp., College Station, TX, USA).

RESULTS

The electronic searches identified a total of 508 titles and abstracts, and we requested the full text of 44 studies (Table 2).

TABLE 2. Results of the Electronic Search

	PUBMED	Medline	CENTRAL
Botulinum toxin AND esotropia	174	54	1
Botulinum toxin AND strabismus	508	493	1
Botulinum toxin AND esotropia AND surgery	-	29	-

We included a total of 9 studies that matched the inclusion criteria for analysis.

Description of Studies

Details of the 9 included studies can be found in Table 3. Scott et al.⁸ treated 413 children ranging in age from 2 months to 12 years with all types of strabismus. The doses of BT varied from 1 to 2.5 IU based on the degree of deviation. If a subsequent injection was required, the dose was increased up to double the prior dose. We selected the group of infantile esotropes with no prior operation (61 children) for analysis. Patients were treated at a mean age of 25 months. The preinjection deviation was 43 PD and 66% of the patients were within 10 PD of orthotropia in the last follow up (mean 29 months). By the end of the study, 25% of this group required surgery.

In a more recent study, de Alba Campomanes et al.¹¹ compared BT with surgery as the primary treatment of infantile esotropia. We analyzed only the BT group (322 children). Injections of 5 IU of botulinum toxin (Botox; Allergan, Irvine, CA, USA) were performed in deviations of less than 50 PD and 7.5 IU in deviations greater than 50 PD. Success rate was 45% after a mean number of injections of 1.6. According to the authors, the most important predictor of alignment in the BT group was the pretreatment magnitude of deviation. In those patients with an esotropia of 30 PD or less, the success rate of botulinum toxin was similar to surgery. On the other hand, stratification by preoperative deviation revealed that among subjects with strabismus bigger than 30 PD, surgery achieved 72% success and BT 36% (risk ratio, 2.0; 95% CI, 1.5–2.7). From the BT group, 74 (22.9%) underwent surgery for under-correction, and four patients who were aligned in primary gaze had surgery to correct dissociated vertical deviation or oblique muscle overaction. No patients in this group had surgery to correct consecutive exotropia.

McNeer et al.¹² studied 76 children submitted to 2.5 IU of botulinum toxin (Botox; Allergan, Irvine, CA, USA) trans-conjunctival injection with the use of an electromyographic monitor. The authors divided the patients in two groups according to age at injection. For statistical analysis, we considered the groups separately (groups A and B). Patients who received the BT before 12 months of age (mean 7.8 months) had a success rate of 93%, while patients older than 12 months (mean 25.6 months) had a success rate of 86%. The mean follow-up was 36 months.

Benabent et al.¹³ studied 40 children with essential infantile esotropia. They were submitted to the injection of 7 IU of botulinum toxin (Botox; Allergan, Dublin, Ireland) in the medial recti without electromyographic assistance. The mean initial deviation was 25.8 PD and 6 months after the injection it reduced to an average of 8.5 PD (success rate 53%). Ptosis was present in 23% of the injected eyes. It was transient and lasted less than 3 months in all patients.

Campos et al.¹⁴ evaluated the results of BT performed under direct visualization with an “open sky” technique in 60 children with essential infantile esotropia. Mean age at injection was 6.5 months. Average follow-up was 5.2 years and success rate was 88% after a single treatment. All patients

TABLE 3. Characteristics of Included Studies

Study	Patients, n	Success Rate, %	Mean Follow up	Consecutive XI, %	Ptosis, %	Vertical Deviation, %	Mean Age, mo	Preop Deviation	Variation on Deviation	Dose, IU	Mean Number of Injections
No. 1: Scott et al. ⁸	61	66.0	29.0	-	31.0	16.0	25.00	43.00	-33.00	-	2.20
No. 2: de Alba Campomanes et al. ¹¹	322	45.0	22.6	2.8	-	-	16.69	38.80	-	-	1.60
No. 3A: McNeer et al. ¹²	41	93.0	36.5	-	-	-	7.80	36.30	-34.60	2.50	2.00
No. 3B: McNeer et al. ¹²	35	86.0	36.5	-	-	-	25.60	30.00	-27.70	2.50	1.50
No. 4: Benabent et al. ¹³	40	53.0	6.0	-	23.0	21.0	21.60	25.80	-17.30	7.00	1.00
No. 5: Campos et al. ¹⁴	60	88.0	62.4	0.0	20.0	-	6.50	35.50	-	3.00	1.00
No. 6A: McNeer et al. ¹⁵	27	100.0	12.0	0.0	47.0	-	7.00	43.00	-42.00	2.50	2.00
No. 6B: McNeer et al. ¹⁵	30	100.0	12.0	0.0	-	-	25.00	31.00	-29.00	2.50	1.60
No. 7: Scott et al. ¹⁶	58	66.0	30.0	-	31.0	16.0	23.00	43.00	-31.00	-	2.10
No. 8: Cheng et al. ¹⁷	24	37.5	6.0	-	20.8	2.1	35.80	33.90	-18.00	-	1.00
No. 9: Gursoy et al. ¹⁸	25	68.0	84.0	0.0	32.0	-	10.00	40.60	-	4.00	1.40

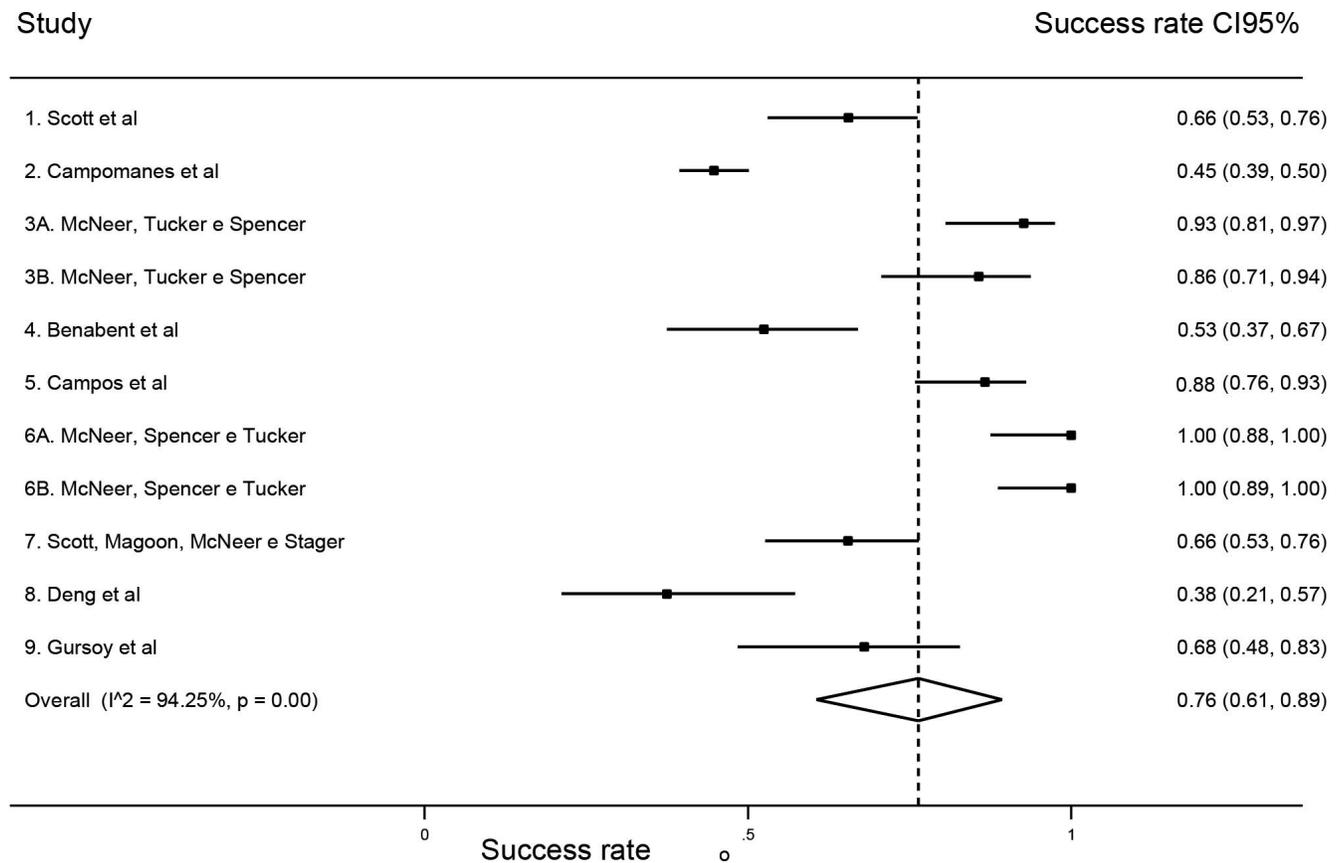


FIGURE 1. Grouped success rate.

developed a transient exotropia 1 to 2 weeks after the procedure. A total of 20% of all the injected eyes developed transient ptosis.

In 1994, McNeer et al.¹⁵ reported the results in 57 patients followed for a mean time of 12 months. As the authors analyzed two subgroups according to the age when BT injection was performed, here we also considered the results separately for statistical analysis. The dose of 2.5 IU of botulinum toxin was injected guided by an electromyographic monitor. Both subgroups (BT performed before and after 12 months of age) had 100% of success in the alignment correction.

In another research, Scott et al.¹⁶ evaluated 356 children treated between 2 months and 12 years. Dosages varied from 1 to 12.5 IU according to angle of deviation. We analyzed the group treated for infantile esotropia with no previous surgery (58 children). Approximately 2.1 injections were required to achieve 66% of success rate.

Chen et al.¹⁷ compared the results of BT combined or not with sodium hyaluronate. We only included in the analysis the group in which BT was injected alone. A total of 24 cases were treated with one injection of 2.5 to 3.75 IU of botulinum toxin (Botox; Lanzhou Institute of Biological Products, Lanzhou, China) without electromyography at a mean age of 35.8 months. Six months after the procedure, 37.5% of the patients presented good alignment.

Lastly, Gursoy et al.¹⁸ performed a prospective report. They compared the results of BT injection versus muscle surgery to treat infantile esotropia. A total of 25 patients were submitted to BT at a mean age of 10 months. After a mean follow-up time of 84 months and an average of 1.4 injections, 68% of the patients achieved successful alignment.

Statistical Analysis

Due to the substantial heterogeneity observed in the results, the success rate, the complications, and the deviation change were presented using a random model. Subsequently, meta-regression models were fitted to identify possible sources of heterogeneity between the estimations.

The grouped success rate of botulinum toxin treatment in infantile esotropia was 76% (95% confidence interval [CI]: 61%–89%; Fig. 1). For the success rate, I^2 of 94.25% was observed, indicating a high heterogeneity ($P < 0.001$). Studies 1, 7, and 9 presented similar rates (between 66% and 68%), as did studies 3B and 5 (86% and 87%, respectively). On the other hand, study 8 had the lowest success rate (38%) and study 6 (A and B), 100% of success. We attempted to identify the possible causes of heterogeneity by considering the means of the age, initial deviation, mean number of injections, follow-up time, and sample size via meta-regression. Univariate and multivariate models were adjusted and are presented on Table 4. There was no association between the success rates and the study variables.

Meta-regressions were adjusted for the seven studies that performed the injections with the same dosage of BT (3A, 3B, 4, 5, 6A, 6B, and 9). Due to the number of studies, for the multivariate model we considered the significant predictor variables at 20%.

As shown in Table 5, only the dose remained significant in the multivariate model ($P = 0.025$). Thus, excluding the mean number of injections of the model, we consider the univariate model only with the dose ($P = 0.005$). Therefore, the higher the dose of BT injected, the lower the success rate; every 1 IU increased in the mean dose there was a reduction of 0.10% in the success rate.

TABLE 4. Meta-Regression Results for Success Rate

	Meta-Regression			
	Univariate		Multivariate	
	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value
Mean age	-0.0115 (-0.0267; 0.0038)	0.124	-0.0141 (-0.0319; 0.0037)	0.098
Preop deviation	0.0010 (-0.0274; 0.0293)	0.940	-0.0204 (-0.0588; 0.0180)	0.230
Mean number of injections	0.1613 (-0.1883; 0.5108)	0.324	0.3061 (-0.1660; 0.7782)	0.156
Mean follow up	0.0016 (-0.0053; 0.0085)	0.614	0.0002 (-0.0076; 0.008)	0.953
Number of patients	-0.0011 (-0.0028; 0.0005)	0.160	-0.0011 (-0.0027; 0.0006)	0.156

N = 11.

When correlating the technique used for BT injections and success rates, the injections guided by electromyography revealed higher success rates than the transconjunctival injections with no electromyography (EMG; $P = 0.006$). When EMG and direct visualization injection were compared, there was no statistic difference ($P = 0.89$).

The complication rates were also analyzed. The occurrence of permanent consecutive XT, transient ptosis, and vertical deviation were considered complications. For meta-regressions, age and dose were considered predictors, when possible.

According to Figure 2, only five studies contributed to the analysis of consecutive XT. The grouped consecutive rate of XT was 1% (95% CI: 0%-2%). For this analysis, the I^2 was 0% ($P = 0.490$) indicating homogeneity among the estimates. In four of the five studies, no cases of consecutive XT were reported and one study presented a rate of only 3%. Supporting this, there was no association between the consecutive XT rate and age ($P = 0.435$) via meta-regression. It was not possible to evaluate the dose-effect as the four studies using a single dose (5, 6A, 6B, and 9) had no consecutive XT cases.

Seven studies contributed to the analysis of the occurrence of ptosis. The grouped ptosis rate was 27% (95% CI: 21%-33%; Fig. 3). The value of I^2 was 20% ($P = 0.280$); therefore, the rates of ptosis were not considered heterogeneous. Only the 6A study presented a rate of ptosis higher than 40%, the other studies presented rates ranging from 17% to 32%. By the meta-regression analysis, there was no association between the rate of ptosis and age ($P = 0.654$), as well as the dose of BT injected ($P = 0.581$).

When analyzing the occurrence of vertical deviation, the grouped rate was 12% (95% CI: 4%-22%; Fig. 4). For this analysis, I^2 was 68.1% ($P = 0.020$), showing heterogeneity. Study 8 had no case of this complication, differently from the others that presented rates above 15%. There was no association between the rate of vertical deviation and age ($P = 0.069$) via meta-regression. It was not possible to assess the

effect of the dose as only four studies presented the single dose regardless the dose being smaller or larger.

The mean change of the deviation after BT injection was -30.7 (95% CI: -37.7, -23.8), demonstrating a significant improvement in alignment (Fig. 5). For this analysis, I^2 was 88.1% ($P < 0.001$) denoting that the mean deviation change in the studies was heterogeneous. Adjusting for a meta-regression model and considering age as a predictor variable, it was significant ($P = 0.020$), indicating that the older the child at the time of the procedure, the greater the deviation/increase of 0.65 diopters (95% CI: 0.19, 1.11) at every 1-year increase in mean age, reducing the delta in the deviation. It was not possible to establish dose effect information.

DISCUSSION

Surgical success rates for infantile esotropia have been reported by Scott et al.²² (65%); von Noorden et al.²⁵ (66%); and Issaho et al.²⁴ (59%). Currently most strabismus specialists prefer surgery to other treatments due to the more predictable results in the alignment.

Scott⁶ first described the use of botulinum toxin in the treatment of strabismus in 1980 and afterward several authors also reported their outcomes. However, it remains unclear how effective and predictable the BT is in comparison to other options to treat strabismus.

Nine studies in which BT injection was performed to treat infantile esotropia were included in this analysis. Two reports were subdivided for analysis^{12,15} since the results were provided separately according to age.

All the authors used botulinum toxin, except for Scott et al.^{8,16} who did not specify the type of BT injected. Additionally, some authors used the transconjunctival technique with EMG assistance in the procedures.^{8,12,15,16} Others opted for no EMG assistance.^{11,13,17,18} Campos et al.¹⁴ performed the injections under direct visualization of the muscle.

TABLE 5. Meta-Regression Results for Success Rate Considering a Pattern Dose of Botulinum Toxin

	Meta-Regression			
	Univariate		Multivariate	
	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value
Mean age	-0.0034 (-0.0250; 0.0182)	0.700	-	-
Mean preop deviation	0.0120 (-0.0175; 0.0415)	0.343	-	-
Mean number of injections	0.2635 (-0.0821; 0.6091)	0.107	0.0534 (-0.1735; 0.2803)	0.549
Mean follow up	-0.0011 (-0.0079; 0.0058)	0.706	-	-
Patients, n	-0.0010 (-0.0173; 0.0153)	0.886	-	-
Dose	-0.1019 (-0.1558; -0.048)	0.005	-0.0914 (-0.1644; -0.0184)	0.025

N = 7.

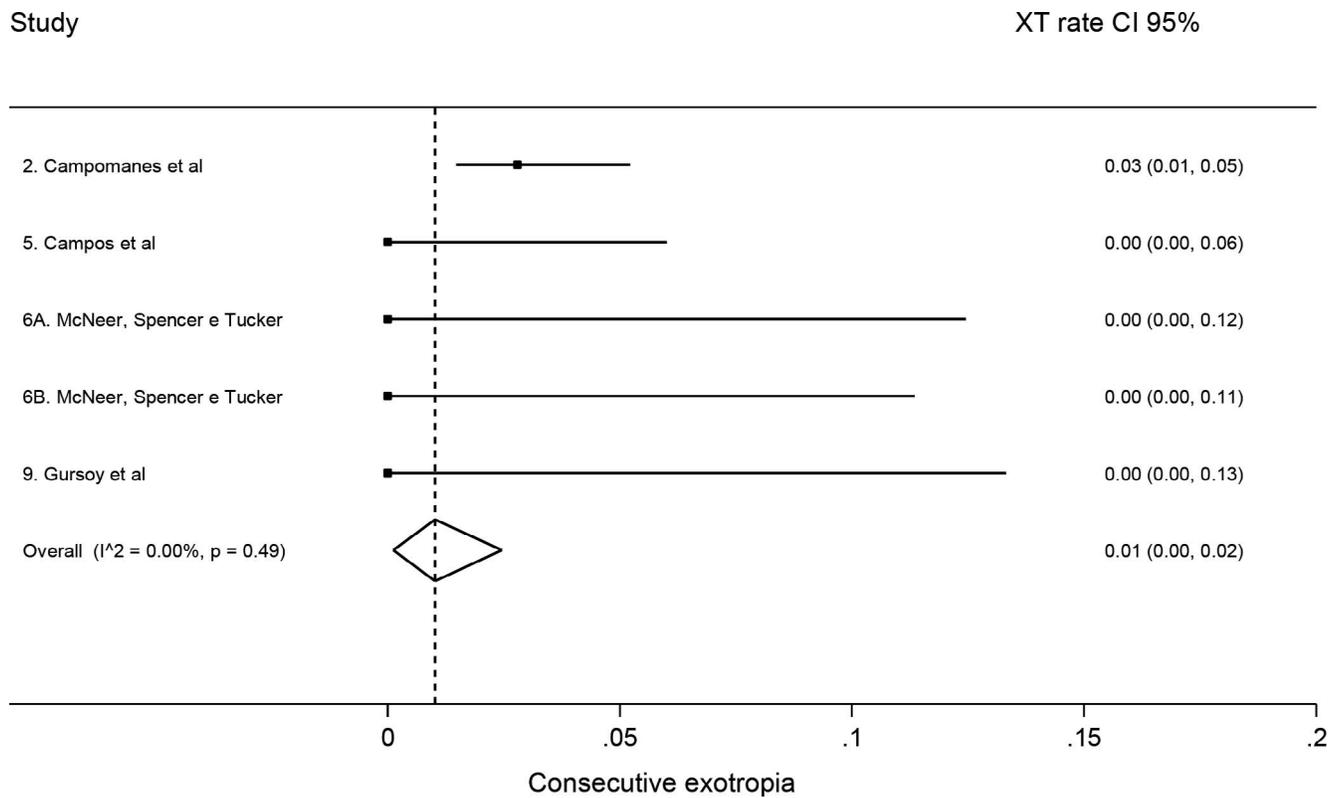


FIGURE 2. Grouped rate of consecutive exotropia.

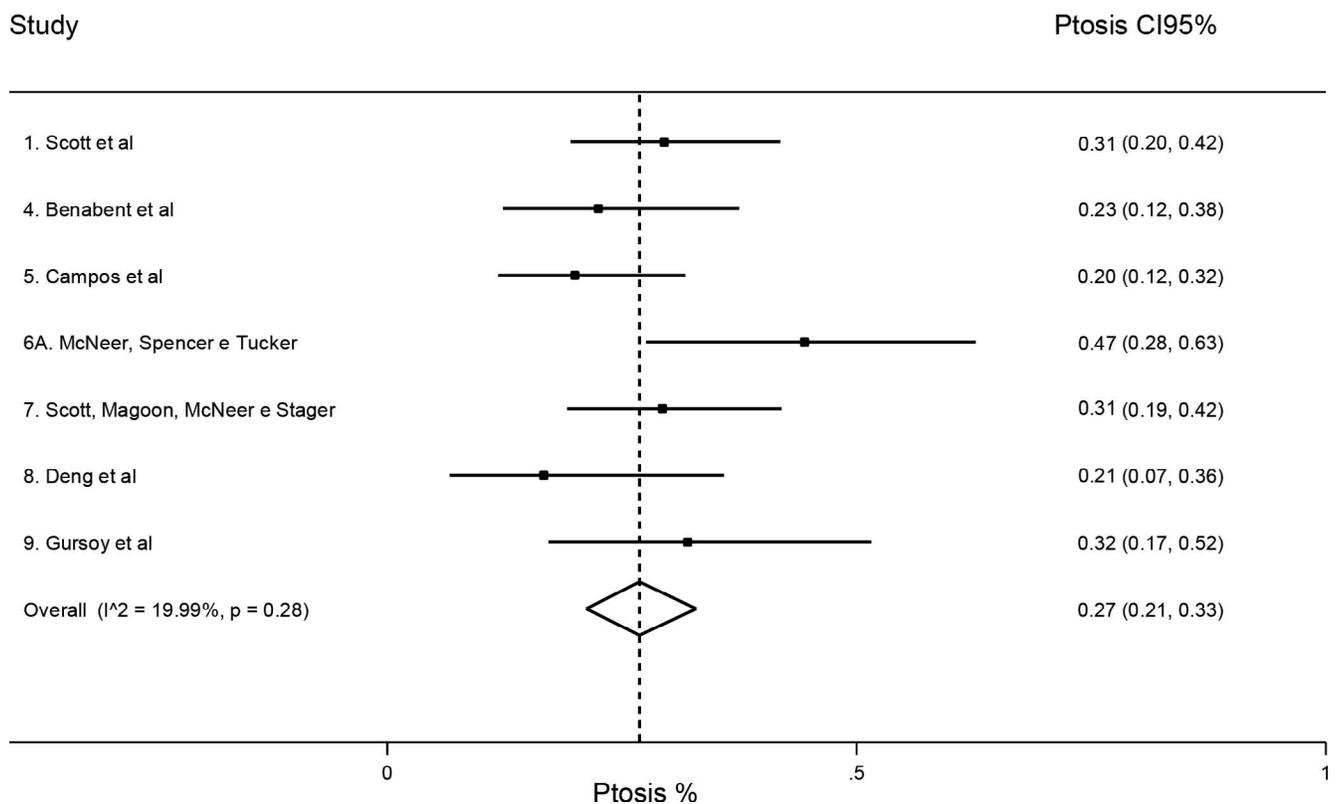


FIGURE 3. Grouped ptosis rate.

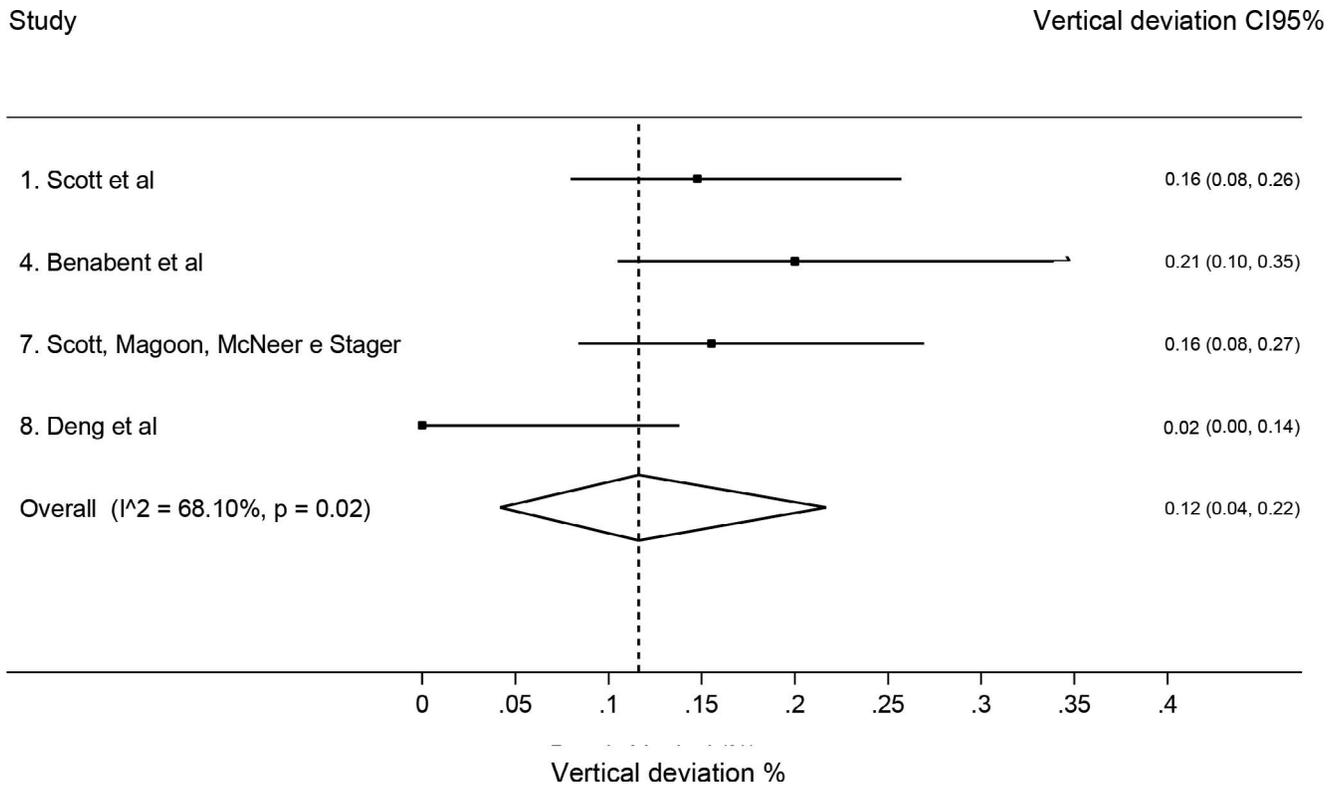


FIGURE 4. Grouped vertical deviation rate.

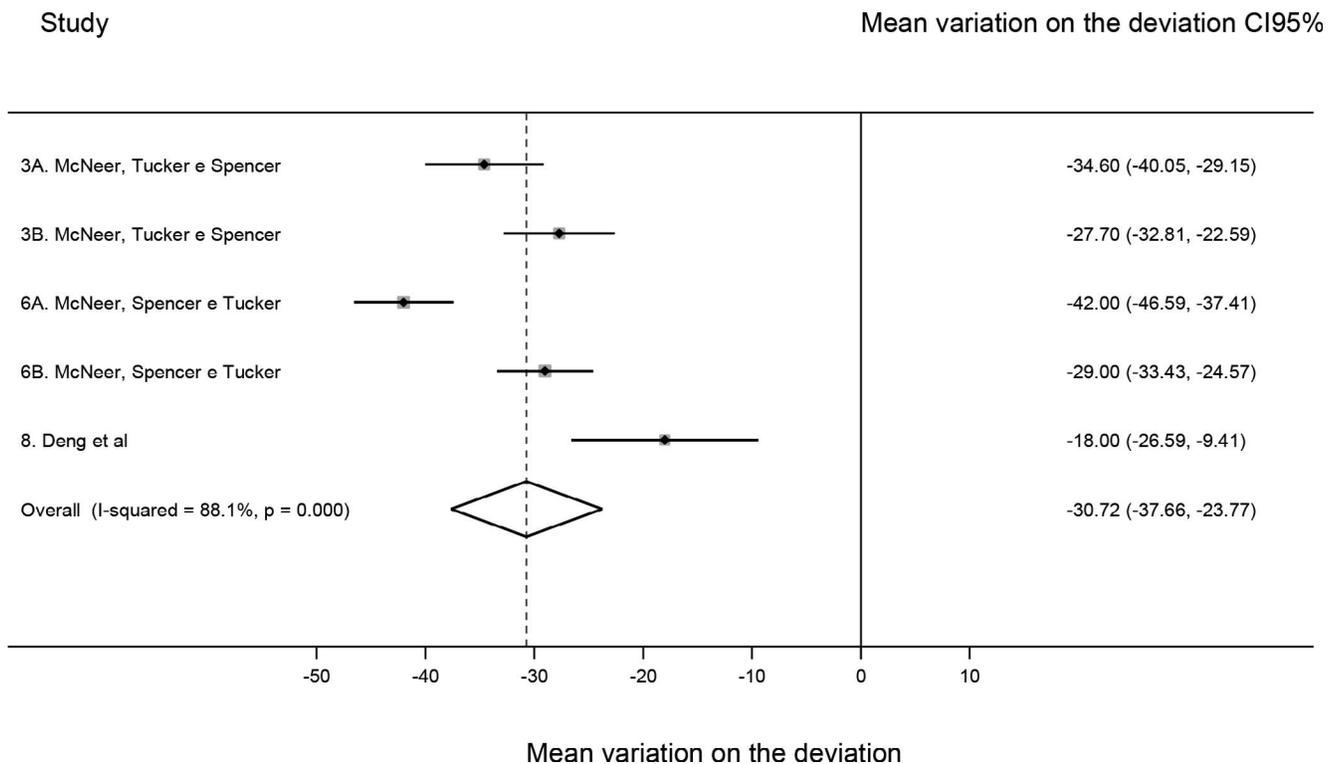


FIGURE 5. Grouped variation of the deviation.

We were able to report the primary outcome of improved ocular alignment by a reduction in the mean deviation in all nine studies. Mean preinjection deviation was 38 PD, while mean postinjection deviation was 6.25 PD. The average number of injections was 1.4. The grouped success rate of BT injection was 76%, but we did observe a high heterogeneity in the studies (I^2 statistics: 94.25%). It was not possible to evaluate the dose response of BT across a range of different doses used in some of the studies.

An interesting result was the inverse association between the dose of BT and the success rate. We observed that the higher the dose of BT injected, the lower the success rate—every 1 IU increased in the mean dose there was a reduction of 0.1% in the success rate. Probably this is due to the tendency to use higher doses of BT in bigger angles of deviation. Alba Campomanes et al.¹¹ concluded that BT was most effective for esotropia ranging from 30 to 35 PD, with a success compared to surgery. Success with BT injection when deviation was lower than 30 PD was 51%, while the rate was 39% if deviation was greater than 30 PD. The magnitude of deviation predicted motor outcome when strabismus was treated with BT instead of surgery.

Scott et al.⁸ and de Alba Campomanes et al.¹¹ also analyzed the success rates considering initial angle of deviation (smaller or bigger than 30 PD). They showed better rates in smaller deviations (73% and 59%, respectively) than in bigger esotropias (54% and 36%, respectively).

The average change of the deviation after BT injection was -30.7 , revealing a significant improvement in alignment after the intervention, although the mean deviation change in the studies was heterogeneous. This supports the indication of BT injection as a good alternative to treat moderate esotropia (until 30–35 PD of deviation).

Furthermore, the risk of experiencing anesthesia-related complications in a healthy infant is negligible, but this should still be considered. In addition to the procedural simplicity of botulinum toxin injection, performing it under minimal anesthesia without intubation in a baby is another advantage.^{25,26}

When evaluating the occurrence of complications, the grouped consecutive rate of XT was very low (1%). Hypocorrection is much more frequent than hypercorrection. The overall ptosis rate was 27% with low heterogeneity and vertical deviation rate was 12% with high heterogeneity between groups.

Other less frequent adverse outcomes cited include subconjunctival hemorrhage and diplopia. Inferior oblique overaction and DVD were also observed, but they are naturally associated with infantile esotropia, and not a consequence of the BT injection. Issaho et al.²⁴ reported frequencies of 38% of inferior oblique overaction and 18% of DVD in a large group of children with infantile esotropia submitted to bilateral medial recti recession. Serious complications such as globe perforation did not occur in any of the studies.

Only two authors attempted to analyze the binocular vision. Scott et al.⁸ revealed that of the patients that could be tested for binocularity, several had good motor fusion, but only one third had full stereopsis. Gursoy et al.¹⁸ compared the results of BT injection versus muscle surgery. Binocular vision with Bagolini-striated glasses was detected in 86% of the reliable responders in the BT and 78% in the surgery group. Gross stereopsis was demonstrable in 10 of 15 patients in the botulinum group and 9 of 13 in the surgery group (odds ratio = 3.6, $P = 0.46$). Two patients in the botulinum group achieved stereoacuity of 40 arc seconds.

Our results elucidate many questions currently experienced on the use of botulinum toxin to treat infantile esotropia. However, most of published literature consists of retrospective

studies, case reviews or cohort studies. Although these provide very useful descriptive information, in order to improve the evidence base for the use of botulinum toxin as an independent management alternative, there is a strong necessity for good quality randomized trials to be performed. Standardization is very important, considering the types of botulinum toxin available and especially the different dosages used as these features are not quite comparable. The evaluation of binocular vision is also an important factor to be considered in future trials.

CONCLUSIONS

Botulinum toxin injection into medial recti muscles reveals to be a safe procedure and offers a valuable alternative to strabismus surgery in congenital esotropia, especially in moderate deviations.

Randomized clinical trials are necessary to consolidate the effective use of botulinum toxin as an independent treatment modality.

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References

1. Wright KW, Spiegel PH, eds. Chapter 18: Esotropia. In: *Pediatric Ophthalmology and Strabismus*. Springer Science & Business Media; 2013:281-305.
2. Souza-Dias CR, Goldchmit M. *Os Estrabismos - Teoria e Casos Comentados*. Rio de Janeiro: Cultura Médica, Guanabara Koogan; 2011:103-111.
3. Cole GA, Camuglia JE. Chapter 74: Infantile esotropias. In: Hoyt, Simmons C, Taylor D, eds. *Pediatric Ophthalmology and Strabismus*. Amsterdam: Elsevier Health Sciences; 2012: 764-782.
4. Schworm HD, Rudolph G. Comitant strabismus. *Curr Opin Ophthalmol*. 2000;11:310-317.
5. Wong AM. Timing of surgery for infantile esotropia: sensory and motor outcomes. *Can J Ophthalmol*. 2008;43:643-651.
6. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology*. 1980; 87:1044-1049.
7. Rowe FJ, Noonan CP. Botulinum toxin for the treatment of strabismus. *Cochrane Database Syst Rev*. 2012;2:CD006499.
8. Scott AB, Magoon EH, McNeer KW, Stager DR. Botulinum treatment of childhood strabismus. *Ophthalmology*. 1990;97: 1434-1438.
9. Spencer RF, Tucker MG, McNeer KW, Porter JD. Experimental studies of pharmacological and surgical denervation of extraocular muscles in adult and infant monkeys. In: Scott AB, ed. *The Mechanics of Strabismus: A Symposium on Oculomotor Engineering*. San Francisco, CA: Smith-Kettlewell Eye Research Institute; 1992:207-227.

10. Spencer RF, McNeer KW. Botulinum toxin paralysis of adult monkey extraocular muscle: structural alterations in orbital, singly innervated muscle fibers. *Arch Ophthalmol*. 1987;105:1703-1711.
11. de Alba Campomanes AG, Binenbaum G, Eguiarte GC. Comparison of botulinum toxin with surgery as primary treatment for infantile esotropia. *J AAPOS*. 2010;14:111-116.
12. MacNeer KW, Tucker MG, Spencer RF. Botulinum toxin management of essential infantile esotropia in children. *Arch Ophthalmol*. 1997;115:1411-1418.
13. Benabent EC, García Hermosa P, Arrazola MT, Alió y Sanz JL. Botulinum toxin injection without electromyographic assistance. *J Pediatr Ophthalmol Strabismus*. 2002;39:231-234.
14. Campos EC, Schiavi C, Bellusci C. Critical age of botulinum toxin treatment in essential infantile esotropia. *J Pediatr Ophthalmol Strabismus*. 2000;37:328-332.
15. McNeer KW, Spencer RF, Tucker MG. Observations on simultaneous botulinum toxin injection in infantile esotropia. *J Pediatr Ophthalmol Strabismus*. 1994;31:214-219.
16. Scott AB, Magoon EG, McNeer KW, Stager DR. Botulinum treatment of strabismus in children. *Trans Am Ophthalmol Soc*. 1998;87:174.
17. Chen J, Deng D, Zhong H, et al. Botulinum toxin injections combined with or without sodium hyaluronate in the absence of electromyography for the treatment of infantile esotropia: a pilot study. *Eye (Lond)* 2013;27:382-386.
18. Gursoy H, Basmak H, Sahin A, Yildirim N, Aydin Y, Colak E. 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.
19. Magoon EH. Chemodeneration of strabismic children. A 2- to 5-year follow up study compared with shorter follow-up. *Ophthalmology*. 1989;96:931-934.
20. Ing MR. Botulinum alignment for congenital esotropia. *Ophthalmology*. 1993;100:318-322.
21. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
22. Scott WE, Reese PO, Hirsh CR, Flabetich CA. Surgery for large-angle congenital esotropia: two vs three and four horizontal muscles. *Arch Ophthalmol*. 1986;104:374-377.
23. von Noorden GK. A reassessment of infantile esotropia. XLIV Edward Jackson memorial lecture. *Am J Ophthalmol*. 1988;105:1-10.
24. Issaho DC, Wang SX, de Freitas D, Weakley DR Jr. Variability in response to bilateral medial rectus recessions in infantile esotropia. *J Pediatr Ophthalmol Strabismus*. 2016;53:305-310.
25. McCann ME. Anesthetic neurotoxicity in babies. *J AAPOS*. 2011;15:515-517.
26. Cohenn MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. *Anesth Analg*. 1990;70:160-167.