• Clinical Research •

Botulinum toxin type A in treating early-stage patients with small-angle acute acquired comitant esotropia

Run-Ting Ma, Die-Wen-Jie Hu, Lian-Hong Zhou, Wen-Ping Li, Yuan-Jin Li, Bei-Xi Yi

Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China

Co-first authors: Run-Ting Ma and Die-Wen-Jie Hu

Correspondence to: Lian-Hong Zhou. Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China. zlh681102@aliyun.com

Received: 2024-01-03 Accepted: 2024-03-12

Abstract

● **AIM:** To investigate botulinum toxin A (BTXA) efficacy on small-angle (≤25$^{\Delta}$) acute acquired concomitant esotropia (AACE) in early-stage patients.

● **METHODS:** The electronic medical record data of AACE patients during March 2019 and June 2023 were collected in this retrospective and hospital-based cohort study. A total of 72 small-angle AACE patients received BTXA extraocular muscle injection. Patients were grouped by onset-to-treatment time (Group A: ≤6mo, Group B: >6mo). Deviation of esotropia, eye alignment and stereopsis were analyzed at the period of pre/post-injection (1wk, 1, 3, and 6mo). Orthophoria rate at 6mo (horizontal deviation <10$^{\Delta}$ and binocular single vision) were considered as outcome index.

● **RESULTS:** There were no significant baseline differences (P>0.05) between two groups except onset-to-treatment time (2mo *vs* 11mo, P<0.001). Higher orthophoria rates were in Group A at last follow-up (94.74% *vs* 73.53%, P=0.013). Post-BTXA deviations of two groups at 1mo showed no difference (P>0.05); while in 3 and 6mo Group A was significantly smaller than group B (all P<0.001). No statistically significant differences were observed among all post-BTXA deviations of near and distance in Group A. In Group B, deviation at 3mo (near: 2$^{\Delta}$ *vs* 0, P<0.001; distance: 4$^{\Delta}$ *vs* 0, P<0.001) and 6mo (near: 6$^{\Delta}$ *vs* 0, P<0.001; distance: 6$^{\Delta}$ *vs* 0, P<0.001) was significant increased compared to deviation at 1wk after treatment. Group A showed better stereopsis recovery in last follow-up compared to Group B (80'' *vs* 200'', P=0.002). Both groups obtained improved stereopsis after treatment (Group A: 80'' *vs* 300'', P<0.001; Group B: 200'' *vs* 300'', P=0.037).

● **CONCLUSION:** BTXA is effective for AACE with small deviation (≤25$^{\Delta}$) in early stage. Delayed treatment (>6mo) may reduce BTXA efficacy. Early BTXA intervention benefits long-term eye alignment and stereopsis recovery.

● **KEYWORDS:** acute acquired comitant esotropia; botulinum toxin type A; stereopsis

DOI:10.18240/ijo.2024.06.15

Citation: Ma RT, Hu DWJ, Zhou LH, Li WP, Li YJ, Yi BX. Botulinum toxin type A in treating early-stage patients with small-angle acute acquired comitant esotropia. *Int J Ophthalmol* 2024;17(6):1094-1101

INTRODUCTION

Acute acquired comitant esotropia (AACE), a relatively uncommon form of esotropia, was initially identified by Burian and Miller in 1958[1]. AACE is characterized by a sudden onset of horizontal diplopia and no significant impairment of eye movements. Mohney[2] reported its prevalence of around 0.3% in childhood strabismus. In recent years, a notable rise in reported cases[3], possibly attributed to the increased use of electronic screens[4-6]. AACE is classified into three types based on etiology and clinical features, with type III (Bielschowsky type) being the most prevalent in contemporary cases[7]. This type commonly affects adolescents and adults and is frequently associated with varying degrees of myopia[8]. The escalating incidence of AACE underscores the importance of research about early intervention. It will be crucial for treatment strategies and stereopsis protection for this intriguing ophthalmic condition.

Contemporary AACE treatments encompass prisms, surgical interventions, and extraocular muscle injections utilizing botulinum toxin A (BTXA). BTXA, with its FDA approval dating back to 1989, had a well-established clinical history in strabismus management. Its versatility extends to treating various ocular conditions, including congenital esotropia, paralytic strabismus, cyclic esotropia, and thyroid-associated ophthalmopathy[9]. In 1999, Dawson *et al*[10] pioneered the exploration of BTXA for AACE treatment in children. The outcomes of these early experiments indicated the efficacy of timely BTXA administration in achieving alignment and potential benefits for binocular visual function. Wan *et al*[11] revealed that the success rate of BTXA was comparable to

surgical interventions while proving to be a more cost-effective alternative.

While BTXA is known for its minimally invasive approach and repeatability, its efficacy in AACE may face challenges like recurrence or subsequent surgery[12-14]. The early instability of deviations in AACE often deters surgical interventions. However, the cases with severe diplopia and rapid stereopsis damage require prompt treatment, leading to a crucial consideration of the appropriate degree range and timing of BTXA injection for AACE in the early stage. The current consensus on BTXA for AACE is imperfect, with limited studies analyzing early intervention effects in patients with small-angle AACE. Our previous study has found that patients with less deviations and shorter time of onset to injection have better outcomes[15]. However, our prior studies primarily focused on individuals with a disease duration of a year or more, and there was a lack of dedicated analysis concerning patients with small-angle AACE. In the current clinical landscape, there is a notable surge in the number of cases involving small-angle AACE, underscoring a compelling demand for targeted interventions.

Through comparing orthophoria rates and follow-up deviations in AACE cases with varying durations from onset to BTXA, the study aims to highlight the benefits of early BTXA application (≤6mo from onset) in patients with small-angle AACE (≤25$^{\Delta}$). This research offers insights into optimizing BTXA use in managing AACE.

SUBJECTS AND METHODS

Ethical Approval The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (WDRY2020-K211) and was conducted according to the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

Study Design and Setting The study was a retrospective cohort study. Information of 72 AACE patients who met the study criteria was selected from medical record system (March 2019-June 2023). Patients were divided into two groups according to the time from onset to treatment: Group A: ≤6mo; Group B: >6mo. The deviations of esotropia, stereopsis and orthophoria rate at final follow-up were observed. To investigate the benefit of timely BTXA treatment after onset in patients with small-angle AACE. All patient information is captured from the health information system. The study used the STROBE cohort reporting guidelines[16].

Subjects The database has been successfully used in previous study about AACE. Because it is objective by using alternate prism cover testing (APCT), patients from 3 different strabismus doctors were selected to avoid bias. Patients with missing information or missing follow-up visits are not included. Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Inclusion and Exclusion Criteria Inclusion criteria: 1) sudden onset of strabismus with a known onset date; 2) accompanied by mainly ipsilateral horizontal diplopia; 3) intermittent or constant; 4) equal strabismus angle in all directions, indicative of concomitant strabismus; 5) deviations ≤25$^{\Delta}$; 6) patients who only received 1 injection were selected for analysis.

Exclusion criteria: 1) strabismus due to craniocerebral diseases; 2) motor neuron or muscular system diseases; 3) paralytic, restrictive, vertical, A/V, or unexplained strabismus; 4) history of strabismus surgery and amblyopia; 5) pregnant or lactating women; 6) allergy to BTXA components; 7) deviation alleviation >10$^{\Delta}$ after cycloplegia; 8) patients with ptosis or the level of strabismus/diplopia existing changes during a day were excluded.

Routine and Ophthalmological Examination Basic information was collected (general health, genetic history, family history, past history), excluding patients with neurological disorders and past history of eye disease. All patients received chest radiographs, electrocardiograms upon admission and ophthalmic examination.

Essential data of ophthalmology encompassed the onset date of strabismus, duration from symptom manifestation to hospital admission, daily near-work duration, characteristics and duration of strabismus and diplopia, and relevant medical/allergy history. Standard ophthalmological assessment incorporated evaluations of both uncorrected visual acuity and best-corrected visual acuity, cycloplegic refraction, intraocular pressure, slit lamp examination, and fundus photography. Strabismus assessments comprised alternate prism cover testing at near and distance, examination of ocular movements (nine-directions photograph), and stereopsis evaluations using the Titmus Book Examination. The alternate prism cover testing was performed at least twice after admission, in the morning and afternoon. Comprehensive CT/MRI scans were universally conducted to exclude neurological disorders. The anatomical position and morphology of the extraocular muscles were observed to exclude strabismus due to thyroid-associated eye disease or heavy eye syndrome and other extraocular muscle degeneration disease. Scheduled follow-ups at 1wk, 1, 3, and 6mo post BTXA extraocular muscle injection encompassed evaluations of strabismus, eye alignment, movements, and stereopsis. The 6-month follow-up duration ensured the thorough dissipation of immediate botulinum toxin effects.

Treatment of Botulinum Toxin A Prior to treatment, patients underwent a comprehensive evaluation by anesthesiologists. Four younger patients (<12y) chose inhalation anesthesia after

Table 1 Characteristics before BTXA Median (range)

Characters	Group A	Group B	U/χ^2	*P*
Patients	38	34	-	-
Sex ratio (male/female)	25/13	17/17	1.841	0.175[a]
Age of onset (y)	27 (16-55)	29 (10-55)	1.040	0.298[b]
Spherical equivalent (D), right	-4.00	-4.38	0.621	0.534[b]
Spherical equivalent (D), left	-3.88	-3.75	1.476	0.140[b]
Near-work time (h/d)	8.5 (4.5-12)	9 (5.5-12)	1.504	0.292[b]
Time from onset to BTXA (mo)	2 (0.5-6)	11 (7-24)	7.346	<0.001[b]

BTXA: Botulinum toxin A. [a]Chi-square test; [b]Wilcoxon test.

Table 2 Comparison of injection doses, types, and orthophoria rates between groups

Parameters	Group A	Group B	U/χ^2	*P*
Orthophoria at 6mo (%)	36/38 (94.74)	25/34 (73.53)	6.235	0.013[a]
Injection dose (U), median (range)	2 (1-3)	2 (1-3)	0.210	0.834[b]
Injection type (unilateral/bilateral)	37/2	29/5	2.021	0.155[a]

[a]Chi-square test; [b]Wilcoxon test.

exclusion of contraindications. The remaining patients were 16 years of age or older and all met the indications for local anesthesia. For adult patients, the subconjunctival infiltration anesthesia was performed by intra conjunctival injection of 2% lidocaine of the operated eye, and 0.01% epinephrine hydrochloride was dropped into the conjunctival sac to constrict the blood vessels. Powdered lyophilized crystals of botulinum toxin (BOTOX, Allergan) were diluted with 2 mL of saline. The corresponding dose of BTXA was withdrawn with a 1 mL syringe (0.02 mL/U). An incision was made in the nasal conjunctiva, and the rectus medialis muscle was hooked. BTXA was injected into the muscle belly 5-6 mm after the muscle stopping point, and no oozing after injection indicated success. Dosage: $<20^{\Delta}$ with 1.0-2.5 U; 20^{Δ}-40^{Δ} with 2.5-4.0 U.

Efficacy Evaluation Efficacy was assessed based on Rowe's criteria for BTXA treatment of strabismus, defining cure as horizontal strabismus $\leq 10^{\Delta}$ at the last follow-up, with the absence of diplopia and the achievement of binocular monovision[17].

Statistical Analysis Statistics analyses were performed using SPSS 22.0. Non-normally distributed data were expressed using the median (range). Wilcoxon test was used for nonparametric tests for between and within-group comparisons. Repeated measures data were compared using the Friedman test. The Chi-square test was used for the comparison of rates. Statistical significance was defined as $P<0.05$.

RESULTS

Characteristics of the Subjects A total of 198 AACE patients in the system were screened and 72 eligible patients were finally included (42 males and 30 females). The study cohort

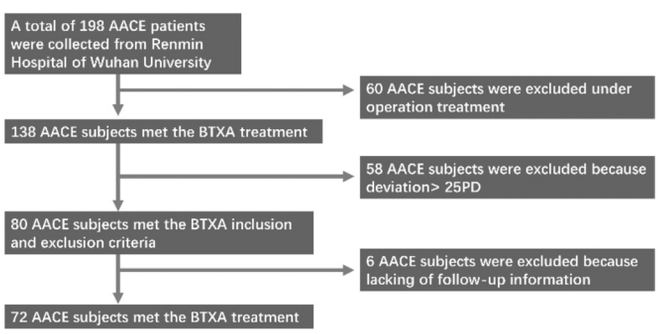

Figure 1 Cohort flow diagram of the study AACE: Acute acquired concomitant esotropia; BTXA: Botulinum toxin A; PD: Prism diopter.

flow diagram is shown in Figure 1. The median age was 28y (range: 10-55), and the median daily near-work time was 9h (range: 4.5-12.0). The median spherical equivalent was -4.25 D of right eye (range: -13.75 to +1.75) and -3.75 D of left eye (range: -14.00 to +1.00). There were no statistically significant differences in gender ratio, age, spherical equivalent, or near-work time between Groups A and B ($P>0.05$). Group A exhibited a significantly shorter median time from onset to treatment than Group B (2mo *vs* 11mo, $P<0.001$; Table 1).

Orthophoria Rates at Final Follow-up There were no differences in injection doses ($P=0.834$) and types (37/2 *vs* 29/5, $P=0.155$) between Groups A and B (Table 2). The 36 patients in Group A [94.74%, 95% confidence interval (CI): 87.3%-100%] and 25 patients in Group B (73.53%, 95%CI: 57.9%-89.2%) were orthophoria after 6mo ($\chi^2=6.235$, $P=0.013$).

Deviations Difference after Botulinum Toxin A Treatment There were no significant difference in median deviations between Groups A and B before, 1wk, and 1mo after treatment; while in 3 and 6mo after treatment Group A was significantly smaller than group B (all $P<0.001$).

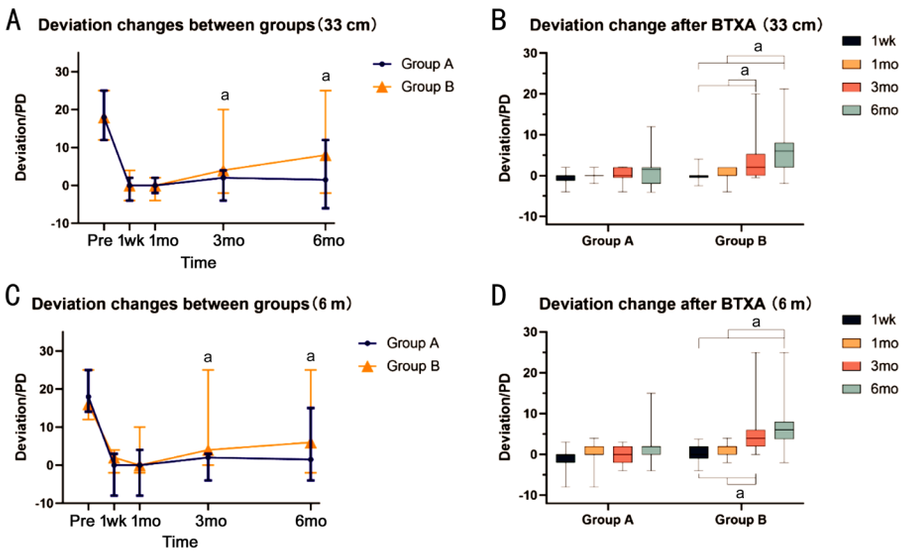

Figure 2 Changes of deviations before and after BTXA treatment A: Changes of near deviations (33 cm) before and after treatment in two groups; B: Comparisons of near deviations (33 cm) within groups after BTXA treatment; C: Changes of distance deviations (6 m) before and after treatment in two groups; D: Comparisons of distance deviations (6 m) within groups after BTXA treatment. PD: Prism diopter; BTXA: Botulinum toxin A. [a]*P*<0.001.

Table 3 Comparison of near deviations (33 cm) at pre- and post-BTXA median (range), PD

Group	Pre-BTXA	Post-BTXA				Friedman test	*P*
		1wk	1mo	3mo	6mo		
A	18 (12, 25)	0 (-4, 2)[a]	0 (-2, 2)[a]	2 (-4, 4)[a]	1.5 (-6, 12)[a]	92.415	<0.001
B	18 (12, 25)	0 (-4, 4)[a]	0 (-4, 2)[a]	2 (-2, 20)[a,b,c]	6 (-2, 25)[a,b,c]	100.336	<0.001
Wilcoxon test	0.739	1.076	0.507	4.093	3.983	-	-
P	0.460	0.282	0.612	<0.001	<0.001	-	-

[a]*P*<0.05 compared with pre-BTXA; [b]*P*<0.05 compared with 1wk post-BTXA; [c]*P*<0.05 compared with 1mo post-BTXA. PD: Prism diopter; BTXA: Botulinum toxin A.

Table 4 Comparison of distance deviations (6 m) at pre- and post-BTXA median (range), PD

Group	Pre-BTXA	Post-BTXA				Friedman test	*P*
		1wk	1mo	3mo	6mo		
A	18 (14, 25)	0 (-8, 3)[a]	0 (-8, 4)[a]	0 (-4, 3)[a]	2 (-4, 15)[a]	93.862	<0.001
B	16 (12, 25)	0 (-4, 6)[a]	2 (-2, 4)[a]	4 (0, 25)[a,b,c]	6 (-2, 25)[a,b,c]	115.612	<0.001
Wilcoxon test	1.525	1.501	1.519	6.182	5.075	-	-
P	0.127	0.133	0.129	<0.001	<0.001	-	-

[a]*P*<0.05 compared with pre-BTXA; [b]*P*<0.05 compared with 1wk post-BTXA; [c]*P*<0.05 compared with 1mo post-BTXA. PD: Prism diopter; BTXA: Botulinum toxin A.

In Group A, the deviation significant decreased after BTXA treatment (near: Friedman test=92.415, *P*<0.001; distance: Friedman test=93.862, *P*<0.001). Pairwise comparisons revealed significant deviations differences between pre-BTXA and 1wk (both near and distance: 18^{Δ} *vs* 0, *P*<0.001), 1mo (both near and distance: 18^{Δ} *vs* 0, *P*<0.001), 3mo (near: 18^{Δ} *vs* 2^{Δ}, *P*<0.001; distance: 18^{Δ} *vs* 0, *P*<0.001), and 6mo (near: 18^{Δ} *vs* 1.5^{Δ}, *P*<0.001; distance: 18^{Δ} *vs* 2^{Δ}, *P*<0.001) after treatment, respectively. However, no statistically significant differences were observed among all post-BTXA deviations of near and distance (*P*>0.05).

In Group B, the deviation significant also decreased after BTXA treatment (near: Friedman test=100.336, *P*<0.001; distance: Friedman test=115.612, *P*<0.001). Pairwise comparisons revealed significant deviations differences between pre-BTXA and 1wk (near: 18^{Δ} *vs* 0, *P*<0.001; distance: 16^{Δ} *vs* 0, *P*<0.001), 1mo (near: 18^{Δ} *vs* 0, *P*<0.001; distance: 16^{Δ} *vs* 2^{Δ}, *P*<0.001), 3mo (near: 18^{Δ} *vs* 2^{Δ}, *P*<0.001; 16^{Δ} *vs* 4^{Δ}, *P*=0.004), and 6mo (near: 18^{Δ} *vs* 6^{Δ}, *P*<0.001; distance: 16^{Δ} *vs* 6^{Δ}, *P*<0.001) after treatment, respectively. Deviation post-BTXA at 3mo (near: 2^{Δ} *vs* 0, *P*<0.001; distance: 4^{Δ} *vs* 0, *P*<0.001) and 6mo (near: 6^{Δ} *vs* 0, *P*<0.001; distance: 6^{Δ} *vs* 0, *P*<0.001) was significant increased compared to deviation at 1wk after treatment (Figure 2, Tables 3 and 4).

Table 5 Comparison of stereopsis in both groups median (range)

Stereopsis	Group A	Group B	U^a	*P*
Pre-BTXA	300'' (50''-800'')	300'' (40''-Nil)	0.740	0.459
Post-BTXA 6mo	80'' (40''-400'')	200'' (40''-Nil)	3.086	0.002
U^a	5.312	2.087	-	-
P	<0.001	0.037	-	-

[a]Wilcoxon test. Nil: More than 800''; BTXA: Botulinum toxin A.

Comparison of Stereopsis Between Two Groups There was no difference of stereopsis between two groups before treatment (*P*=0.459). Both groups demonstrated improved stereopsis after treatment (Table 5). However, Group A showed a better stereopsis recovery at the final follow-up, compared with Group B (*P*=0.002).

Complications There were not statistical difference between the complications in two groups of 1wk after treatment (73.7% *vs* 70.6%, *P*=0.768; Table 6). Symptoms resolved 1mo post-BTXA in patients with ptosis (*n*=5) and 3mo post-BTXA in vertical strabismus cases (*n*=3, <10$^{\Delta}$). The most prevalent complication after injection was exotropia (*n*=10), yet symptoms resolved for the majority of patients in the final follow-up, with small exotropia (<10$^{\Delta}$) persisting in 4 patients without symptoms. One patient experienced limited eye movement after injection, but symptoms completely resolved within 3mo.

Table 6 Complications 1wk after treatment *n* (%)

Complications	Group A	Group B
Ptosis	3/38 (7.8)	3/34 (8.8)
Vertical strabismus	1/38 (2.6)	2/34 (5.9)
Transient exotropia	6/38 (15.8)	4/34 (11.8)
Movement limitation	0	1/34 (2.9)
Without complications	28/38 (73.7)	24/34 (70.6)

χ^2=1.824, *P*=0.768.

DISCUSSION

This retrospective cohort analysis delves into the influence of varying time intervals from onset to BTXA treatment on efficacy, focusing particularly on individuals with small deviations (≤25$^{\Delta}$) in AACE. All participants underwent a 6-month follow-up after BTXA injection. Stratifying patients into two groups based on the duration of AACE (Group A: ≤6mo, Group B: >6mo), our objective was to elucidate the advantages of prompt treatment post-onset of AACE. The orthophoria rate at the 6-month follow-up served as the primary outcome measure. The 11 patients experienced relapse during the final follow-up, predominantly from Group B (9/11, 81.82%). Notably, patients receiving BTXA within 6mo of AACE onset demonstrated significantly higher success rates (Group A: 94.74% *vs* Group B: 73.53%) and better retention or recovery of stereopsis (from 300'' to 80'') at follow-up. Conversely, those receiving BTXA beyond 6mo post-onset exhibited comparatively limited improvement in stereopsis (from 300'' to 200''). These findings underscore the critical role of timely BTXA intervention in optimizing outcomes for AACE patients. In Group A, the shortest duration from onset to treatment was 2wk, resulting in sustained eye alignment for an extended period post-treatment. Conversely, Group B demonstrated a notable resurgence in deviation (near and distance) at 3mo post-treatment. Notably, among Group A patients, none experienced recurrence whose time from onset to treatment was less than three months.

AACE, once considered a rare form of strabismus, has seen a significant rise in prevalence[18]. Despite its increasing occurrence, the etiology remains unknown, with potential factors including near work, accommodative convergence, fusion function, and physical and psychological stress[4,19-21]. According to Burian and Miller's classification[1], AACE comprises type I (Swan type), type II (Franceschetti type), and type III (Bielschowsky type). Types I and II are often linked to monocular vision loss and traumatic experiences, while type III is prevalent in myopic older children or adults. While intracranial lesions[22], systemic diseases[23], and medications[24-25] can also cause acute-onset esotropia, diagnosing AACE requires comprehensive systemic examinations and imaging tests[26]. Although Burian and Miller's classification is commonly used, some scholars need more support. In 2015, Buch and Vinding[21] proposed a more detailed classification with seven subtypes. In 2003, Spierer[8] reported 10 cases of adult AACE, primarily type III, with all patients being myopic (spherical equivalent: -4.7 D), suggesting a strong association between AACE and myopia. Similarly, Lee and Kim[27] reported 16 predominantly type III patients with a mean spherical equivalent of -2.55 D, highlighting the increasing prevalence of type III AACE in clinical settings. Cai *et al*[28] found that AACE patients were mostly myopic and that supine position and near-distance work without glasses were independent risk factors for AACE. This is similar to the findings in our result, where the patients also had an average near-distance work of up to 8-9h per day.

The use of BTXA in clinical treatment has a longstanding history. In 1980, Scott[29] conducted experiments with BTXA injections in adults with esotropia, discovering a positive

correlation between doses and corrective effects. In 1997, McNeer *et al*[30] treated 76 infants with congenital esotropia using BXTA, achieving a 93% success rate in those treated before age 1, with two-thirds establishing stereopsis over a 3-year follow-up. Campos *et al*[31] similarly reported an 88% success rate in a study of 60 infants with congenital esotropia over an average 5.2-year follow-up. This evidence suggests that BTXA can significantly benefit early-onset or acute esotropia affecting visual function. 1999, Dawson *et al*[10] pioneered BTXA treatment for AACE in children, achieving an overall success rate of 79% after an average follow-up of 22mo.

The current challenge in AACE lies in refining the consensus on early intervention[32-33]. A key question is whether BTXA is universally suitable for all types and degrees of AACE. Typically, AACE presents with moderate or small angles, though a few cases may exceed 50^{Δ}-60^{Δ} or more. More significant deviations often undergo surgical intervention, leaving a gap in BTXA efficacy analysis, particularly for small-angle AACE[34]. Routinely, patients have the option of surgical correction and the stability of the procedure is relatively favorable[35-38]. However, the disadvantage is that it is quite invasive and there is also the potential for secondary surgery. Chen *et al*[39] proposed categorizing AACE into smaller ($<20^{\Delta}$) and larger ($>20^{\Delta}$) groups, emphasizing the need for differentiated clinical features and treatments. While there is no strict prohibition against attempting BTXA treatment for large-angle AACE, established norms and indications suggest its relatively positive efficacy in small to moderate deviations of comitant strabismus ($<40^{\Delta}$)[40]. Previous analyses have not analyzed the efficacy of a range of deviations in isolation, and subjects have often included small deviations as well as large angles of AACE[10-11,13-14,41-42]. Consequently, this study focuses on the clinically prevalent range of AACE with small deviations ($\leq 25^{\Delta}$).

Another critical aspect influencing the efficacy of BTXA in AACE may be the timing of intervention. Type III AACE exhibits considerable variability in onset age, myopia degree, and AC/A ratio[43]. The duration from symptom onset to treatment varies widely across studies, ranging from weeks to years, necessitating a more detailed exploration in research. Dawson *et al*'s[10] study revealed that timely BTXA injections within 8wk of onset resulted in favorable outcomes, with 80% of children remaining orthoptic and gradually establishing stereopsis. Similarly, Wan *et al*[11] reported an average onset-to-treatment duration of 3mo, while Xu *et al*[42] observed a success rate of 82.8% at a 6-month follow-up, with onset-to-treatment ranging from 1 to 96wk. These findings collectively suggest that early BTXA application is practical in AACE treatment. Chen *et al*[44] found a compensatory increase in the volume of the lateral rectus in patients with AACE by quantitative MRI analysis, which may have arisen in a long-term effort to overcome diplopia. This finding further may bolster the benefits of early treatment, as indicated by our conclusions.

Considering the metabolic pattern of BTXA, its peak impact on extraocular muscles typically occurs around one week post-injection[45]. In alignment with this, our study observed a significant improvement in patients' eye alignment at the one-week follow-up, occasionally with mild overcorrection. The general mechanism of BTXA action continues for approximately 3mo, during which most corrected eye positions tend to maintain orthophoria after the drug's effects have dissipated[29-30,46]. This sustained effect is thought to be linked to factors such as muscle atrophy, enhanced fusion mechanisms, and relief of muscle tension[46]. The time from onset to treatment might influence these factors, impacting the maintenance effect of BTXA. While most patients remained well-aligned at the final follow-up, those with delayed treatment (>6mo from onset) exhibited a tendency toward deviation rebound in between-group and within-group comparisons. In Group B, statistically significant recovery of esotropia was noted at 3 and 6mo post-injection, compared to the alignment observed 1wk after treatment.

Our study is not without limitations, notably the relatively short follow-up period for patients. Specifically, those in group B demonstrated a notable inclination towards recurrence during the late follow-up phase, potentially necessitating further interventions such as re-injection or surgery in the future. Extending the duration of follow-up could provide a more comprehensive understanding of the metabolic characteristics and durability of BTXA treatment. Additionally, the sample size of our cohort may be considered relatively small, warranting a larger number of cases for robust analysis in subsequent studies. Methodologically, while our study adopts a cohort design, it is inherently retrospective in nature. Thus, future research endeavors may benefit from prospective designs with adequately powered sample sizes to thoroughly elucidate the efficacy of BTXA for AACE.

In conclusion, BTXA is a viable and effective option for treating AACE. The sustained efficacy of BTXA in maintaining eye alignment shows a declining trend over time, potentially linked to the time from onset to BTXA treatment. Provided contraindications are excluded, individuals with small-angle AACE stand to benefit from early-stage BTXA treatment (≤6mo from onset).

ACKNOWLEDGEMENTS

Authors' contributions: Ma RT: concept and editing of the manuscript, conduction of the study, data collection, data analysis, and preparation of manuscript. Hu DWJ: implementing the study, acquisition of data, conduction of the

study, data analysis. Zhou LH: funding acquisition, concept and editing of the manuscript, supervision and revision of the article. Li WP: data collection, data analysis. Li YJ: implementing the study, collecting data. Yi BX: conducted the research, collected the data.

Foundations: Supported by Key Research and Development Program of Hubei Province (No.2022BCA044); the Central Guided Local Science and Technology Development (No.2019ZYYD058).

Conflicts of Interest: Ma RT, None; **Hu DWJ,** None; **Zhou LH,** None; **Li WP,** None; **Li YJ,** None; **Yi BX,** None.

REFERENCES

1 Burian HM, Miller JE. Comitant convergent strabismus with acute onset. *Am J Ophthalmol* 1958;45(4 Pt 2):55-64.

2 Mohney BG. Common forms of childhood strabismus in an incidence cohort. *Am J Ophthalmol* 2007;144(3):465-467.

3 Nouraeinejad A. The rise of acute acquired comitant esotropia. *J Binocul Vis Ocul Motil* 2023;73(4):165-166.

4 Neena R, Remya S, Anantharaman G. Acute acquired comitant esotropia precipitated by excessive near work during the COVID-19-induced home confinement. *Indian J Ophthalmol* 2022;70(4):1359-1364.

5 Iimori H, Suzuki H, Komori M, Hikoya A, Hotta Y, Sato M. Clinical findings of acute acquired comitant esotropia in young patients. *Jpn J Ophthalmol* 2022;66(1):87-93.

6 Hayashi R, Hayashi S, Machida S. The effects of topical cycloplegics in acute acquired comitant esotropia induced by excessive digital device usage. *BMC Ophthalmol* 2022;22(1):366.

7 Lekskul A, Chotkajornkiat N, Wuthisiri W, Tangtammaruk P. Acute acquired comitant esotropia: etiology, clinical course, and management. *Clin Ophthalmol* 2021;15:1567-1572.

8 Spierer A. Acute concomitant esotropia of adulthood. *Ophthalmology* 2003;110(5):1053-1056.

9 Escuder AG, Hunter DG. The role of botulinum toxin in the treatment of strabismus. *Semin Ophthalmol* 2019;34(4):198-204.

10 Dawson EL, Marshman WE, Adams GG. The role of botulinum toxin A in acute-onset esotropia. *Ophthalmology* 1999;106(9):1727-1730.

11 Wan MJ, Mantagos IS, Shah AS, Kazlas M, Hunter DG. Comparison of botulinum toxin with surgery for the treatment of acute-onset comitant esotropia in children. *Am J Ophthalmol* 2017;176:33-39.

12 Li Y, Tong L, Chen Y, Zhang B, Wan M, Yin X, Zhang F. The efficacy of botulinum toxin type A treatment and surgery for acute acquired comitant esotropia. *Front Med* 2023;10:1219419.

13 Lang LJ, Zhu Y, Li ZG, Zheng GY, Peng HY, Rong JB, Xu LM. Comparison of botulinum toxin with surgery for the treatment of acute acquired comitant esotropia and its clinical characteristics. *Sci Rep* 2019;9(1):13869.

14 Tong L, Yu X, Tang X, Zhang Y, Zheng S, Sun Z. Functional acute acquired comitant esotropia: clinical characteristics and efficacy of single Botulinum toxin type A injection. *BMC Ophthalmol* 2020;20(1):464.

15 Huang XQ, Hu XM, Zhao YJ, Ye MH, Yi BX, Zhou LH. Clinical efficacy of botulinum toxin type A on acute acquired comitant esotropia. *Int J Ophthalmol* 2022;15(11):1845-1851.

16 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147(8):573-577.

17 Bort-Martí AR, Rowe FJ, Ruiz Sifre L, Ng SM, Bort-Martí S, Ruiz Garcia V. Botulinum toxin for the treatment of strabismus. *Cochrane Database Syst Rev* 2023;3(3):CD006499.

18 Okita Y, Kimura A, Masuda A, Mochizuki Y, Kondo M, Yamadera K, Gomi F. Yearly changes in cases of acute acquired comitant esotropia during a 12-year period. *Graefes Arch Clin Exp Ophthalmol* 2023;261(9):2661-2668.

19 Vagge A, Giannaccare G, Scarinci F, Cacciamani A, Pellegrini M, Bernabei F, Scorcia V, Traverso CE, Bruzzichessi D. Acute acquired concomitant esotropia from excessive application of near vision during the COVID-19 lockdown. *J Pediatr Ophthalmol Strabismus* 2020;57:e88-e91.

20 Zhao S, Hao J, Liu J, Cao K, Fu J. Fusional vergence dysfunctions in acute acquired concomitant esotropia of adulthood with myopia. *Ophthalmic Res* 2023;66(1):320-327.

21 Buch H, Vinding T. Acute acquired comitant esotropia of childhood: a classification based on 48 children. *Acta Ophthalmol* 2015;93(6):568-574.

22 Nouraeinejad A. Neurological pathologies in acute acquired comitant esotropia. *Graefes Arch Clin Exp Ophthalmol* 2023;261(12):3347-3354.

23 Nouraeinejad A. Neurological pathologies associated with acute acquired comitant esotropia. *Int J Neurosci* 2023:1-2.

24 Hentschel SJ, Yen KG, Lang FF. Chiari I malformation and acute acquired comitant esotropia: case report and review of the literature. *J Neurosurg* 2005;102(4 Suppl):407-412.

25 Parentin F, Marchetti F, Faleschini E, Tonini G, Pensiero S. Acute comitant esotropia secondary to idiopathic intracranial hypertension in a child receiving recombinant human growth hormone. *Can J Ophthalmol* 2009;44(1):110-111.

26 Dragomir MS, Merticariu M, Merticariu CI. Management of acute acquired comitant esotropia in children. *Rom J Ophthalmol* 2023;67(1):87-91.

27 Lee HJ, Kim SJ. Clinical characteristics and surgical outcomes of adults with acute acquired comitant esotropia. *Jpn J Ophthalmol* 2019;63(6):483-489.

28 Cai J, Lai WX, Li X, Li Q, Cai Y, Chen JM. Analysis of independent risk factors for acute acquired comitant esotropia. *Int J Ophthalmol* 2023;16(11):1854-1859.

29 Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* 1980;87(10):1044-1049.

30 McNeer KW, Tucker MG, Spencer RF. Botulinum toxin management of essential infantile esotropia in children. *Arch Ophthalmol* 1997;115(11):1411-1418.

31 Campos EC, Schiavi C, Bellusci C. Critical age of botulinum toxin treatment in essential infantile esotropia. *J Pediatr Ophthalmol Strabismus* 2000;37(6):328-332; quiz 354-355.

32 Nouraeinejad A. To prioritize treatment options for acute acquired comitant esotropia. *Eur J Ophthalmol* 2023;33(4):NP145-NP146.

33 Sheth J, Goyal A, Natarajan D, Warkad VU, Sachdeva V, Kekunnaya R. Clinical profile, neuroimaging characteristics, and surgical outcomes of patients with acute acquired non-accommodative comitant esotropia. *J Pediatr Ophthalmol Strabismus* 2023;60(3):218-225.

34 Yu X, Pan W, Tang X, Zhang Y, Lou L, Zheng S, Yao K, Sun Z. Efficacy of augmented-dosed surgery versus botulinum toxin A injection for acute acquired concomitant esotropia: a 2-year follow-up. *Br J Ophthalmol* 2023:bjo-2023-323646.

35 Lim SH, Lee YG, Kim US. Non-adjustable surgery for acute acquired comitant esotropia under general anesthesia. *BMC Ophthalmol* 2022;22(1):416.

36 Merino P, Freire M, Yáñez-Merino J, Gómez de Liaño P. Surgical outcomes of acquired acute comitant esotropia. Causes and classification. *Arch Soc Esp Oftalmol* 2022;97(10):558-564.

37 Kim DH, Noh HJ. Surgical outcomes of acute acquired comitant esotropia of adulthood. *BMC Ophthalmol* 2021;21(1):45.

38 Zhou Y, Ling L, Wang X, Jiang C, Wen W, Zhao C. Augmented-dose unilateral recession-resection procedure in acute acquired comitant esotropia. *Ophthalmology* 2023;130(5):525-532.

39 Chen J, Deng D, Sun Y, Shen T, Cao G, Yan J, Chen Q, Ye X. Acute acquired concomitant esotropia: clinical features, classification, and etiology. *Medicine (Baltimore)* 2015;94(51):e2273.

40 American Academy Ophthalmology. *Pediatric Ophthalmology and Strabismus.* 2017–2018 BCSC Basic and Clinical Science Course™.

41 Kothari M. Clinical characteristics of spontaneous late-onset comitant acute nonaccommodative esotropia in children. *Indian J Ophthalmol* 2007;55(2):117-120.

42 Xu H, Sun W, Dai S, Cheng Y, Zhao J, Liu Y, Wang J, Wang Y, Gao Y, Han H, Han A. Botulinum toxin injection with conjunctival microincision for the treatment of acute acquired comitant esotropia and its effectiveness. *J Ophthalmol* 2020;2020:1702695.

43 Ruatta C, Schiavi C. Acute acquired concomitant esotropia associated with myopia: is the condition related to any binocular function failure? *Graefes Arch Clin Exp Ophthalmol* 2020;258(11):2509-2515.

44 Chen JY, Zhang LR, Liu JW, Hao J, Li HX, Zhang QY, Liu ZH, Fu J. Magnetic resonance imaging of extraocular rectus muscles abnormalities in acute acquired concomitant esotropia. *Int J Ophthalmol* 2024;17(1):119-125.

45 Dutton JJ, Fowler AM. Botulinum toxin in ophthalmology. *Surv Ophthalmol* 2007;52(1):13-31.

46 Campos EC. Why do the eyes cross? A review and discussion of the nature and origin of essential infantile esotropia, microstrabismus, accommodative esotropia, and acute comitant esotropia. *J AAPOS* 2008;12(4):326-331.