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The Indications and Outcomes of Botulinum Toxin Treatment for Childhood Esotropia

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Abstract— Introduction: This study aims to analyze the indications, effectiveness and side effects of Botulinum toxin in the management of Childhood Esotropia. Methods: A retrospective study of cases underwent botulinum toxin injection for Esotropia strabismus in King Fahad Armed Force Hospital (KFAFH), Jeddah, Saudi Arabia. From the period 1st of Jan 2014 till 31st Dec 2018. For total of 116 patient. Success was defined as a residual angle of deviation of 10 prism diopter (PD) or less which allows for binocularity for at least 6 months. Result: A total of 81 cases were included. 45 males and 36 females. The mean age at 1st injection was 7.29 with range of 0.58 to 24 year old. The most prevalent diagnosis was partially accommodative esotropia (PAET). the overall success rate was 38.3%(31) with NAET and paralytic ET has the highest success with 76.9%(10) and 100%(2) respectively. Conclusion: Botulinum toxin represents a safe, repeatable alternative to surgery in the management of esotropia type of strabismus. Success rate differs in different diagnoses with NAET scoring the highest.

Keywords: Esotropia, Botulinum, Childhood, Strabismus, Botox, Eye.

1. Introduction:

Strabismus is the term of ocular misalignment; it can present as horizontal, vertical, torsional, or any combination of these[1]. It is a common ocular disorder with prevalence ranging from 1.28% to 5.65% in children[2-7]. The treatment goals for strabismus are to restore the ocular alignment, treat amblyopia, maintain binocularity, and eliminate diplopia[8]. There are numerous methods to treat strabismus; the first step is the correction of refractive errors and management of amblyopia if present[8]. Also, orthoptic exercises and ophthalmic prisms can be sufficient for some types of strabismus[9] but many patients require extra ocular surgery (strabismus surgery) in order to improve ocular alignment.

In late 1970s, Alan Scott introduced the use of botulinum toxin for selective weakening of extraocular muscles[10]. In 1981, Alan Scott concluded that botulinum toxin was safe drug without systemic side effects and its useful therapy for strabismus[11]. Since then, there have been many advances in researches in the field of botulinum toxin use in strabismus. botulinum toxin is neurotoxin produced by the bacterium clostridium botulinum, an anaerobic, gram positive with eight exotoxins; Type A is the most potent toxin. In late 1980s, various studies published the efficacity and safety of botulinum toxin injection in children[12-13].

Botulinum toxin can be used as alternative to surgery in children with small to moderate angle infantile esotropia[14] and for acute acquired concomitant esotropia[15-16]. In Saudi Arabia, one study conducted in Dhahran Eye Hospital about the indications, success rates and complications of Botulinum toxin for different horizontal strabismus entities. They concluded that botulinum toxin is a cost effective, safe, repeatable alternative to surgery in the management of horizontal strabismus specially partially accommodative esotropia[17].

The aim of this study is to assess the effectiveness, safety and the possible complications associated with using the botulinum toxin in the management of different types of childhood esotropia.

2. Methodology:

Study design, Setting, Population study, Sample:

A Retrospective cohort study was conducted reviewing all data (from Therefor system database) for patient underwent botulinum toxin injections for esotropia at ophthalmology department, King Fahad Armed Force Hospital (KFAFH), Jeddah, Saudi Arabia. From the period 1st of Jan 2014 till 31st Dec 2018. For total of 116 patient.

The exclusion criteria which were: (1) Any botulinum toxin injections performed outside KFAF, (2) Previous strabismus surgeries, (3) Any previous ocular surgeries which can alter the alignment of the eyes like orbital decompression, scleral buckle surgery, (4) Any history of orbital bone fractures, (5) any other types of strabismus.

All patients' files were at least reviewed for 18 months after their last visit to the hospital for the following:

• History: demographic data, detailed history for Strabismus and management

• Complete ophthalmologic and orthoptic assessment: visual acuity, extraocular muscle movements, angle of deviation, slit lamp examination, dilated fundus exam, cycloplegic refraction and spectacle correction.

o The Angle of Deviation: for cooperative patients or 5 years old or older and can maintain fixation we performed prism cover test at near and distance, for uncooperative patient, younger than 5 years or poor vision in one eye we used Krimisky test.

o Visual Acuity: measurement was taken from Snellen Chart, for uncooperative we used central steady maintained (CSM) fixation method.

• Diagnosis, Treatment offered, Follow-ups.

Procedure and dosage:

Following good pre-operative assessment done by anesthesiologist, patients went to the operative room were inhalation anesthesia carried out, the site of injection was selected by experienced ophthalmologist according to the anatomical site of the desired ocular muscle (according to spiral of tillaux).

The dose amount varies according to the deviation:

• Deviation angle of 35 or less, they received 5U.

• Deviation angle Between 35 and 50, they received 7.5U.

• Deviation angle more than 50, they received 10U.

Post injection follow-up:

After receiving the first injection patients were seen at least 2 follow-ups. First is between 2 to 4 weeks and second visit is 6 months post injection. In each visit we measure angle of deviation, which categorized as small (<20PD), moderate (≥20PD and <40PD), and large (≥40PD).

Success was defined as a residual angle of deviation of 10 prism diopter (PD) or less which allows for binocularity for at least 6 months.

For patients who didn't reach or maintain motor fusion for 6 months we give them the chance of the second injection of Botox and follow up similar to first injection, up to the 3rd injection.

For the caregivers who refused the second dose and prefer surgical intervention we offer it for them after explaining the benefits and risks of each procedure.

Also, we prefer surgical intervention rather than continuing Botox injections for the patients who had angle of 20 PD or more post 1st injection as this give us the hint of poor outcome from Botox.

Surgical intervention for horizontal strabismus or a residual angle of deviation more than 12PD after the 3rd injection was considered failure.

Surgical intervention for vertical deviation and inferior oblique over-action (IOOA) was not considered as a failure.

Statistical Analysis:

Numerical data was summarized with mean and standard deviation. Categorical data was summarized with percentages. The success rate was analyzed in regards to amblyopia, baseline angle of deviation, and age using Chi-square with Fisher exact test. All statistical analysis was performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). All figures were created using Microsoft Excel (2019, Microsoft Corp.). A p-value less than 0.05 was considered statistically significant.

Research Ethics:

This study was approved by the Research and ethics committee at KFAFH (Ref: 383).

3. Results:

Eighty-one patients with a diagnosis of esotropia and no history of strabismus surgery received Botulinum Toxin (BOTOX) injections, of whom forty-five were males and thirty-six were females. The mean age at 1st injection was 7.29±4.61 (0.58 to 24). Demographic and clinical characteristics were summarized in Table 1. The onset of esotropia was as early as 1month and as late as 18years with mean age of 2.77±3.01years. The most prevalent type of esotropia (Figure 1) was partially accommodative esotropia PAET (51.9%) followed by non-accommodative esotropia NAET (16%), partially accommodative esotropia with high AC/C ratio (12.3%), and infantile esotropia (12.3%). One patient with sensory esotropia was post traumatic cataract.

Table 1 Demographics and clinical characteristics

Parameter	**Mean± SD (range)**	**Percentage(n)**

Patients		100% (81)
Age at 1st Injection (year)	7.29±4.61 (0.58 to 24)	
Gender		
	Males	55.6% (45)
	Female	44.4% (36)
Medical Illness		
	Free	95.1% (77)
	Ill	4.9% (4)
Type of esotropia		
	PAET	51.9% (42)
	PAET with high AC/A	12.3% (10)
	FAET	2.5% (2)
	NAET	16% (13)
	Infantile ET	12.3% (10)
	Paralytic ET	2.5% (2)
	Sensory ET	2.5% (2)
History of strabismus surgery		0% (0)

ET, esotropia; PAET, partially-accommodative esotropia; AC/A, accommodative convergence to accommodation ratio; FAET, fully-accommodative esotropia; NAET, non-accommodative esotropia; SD, standard deviation.

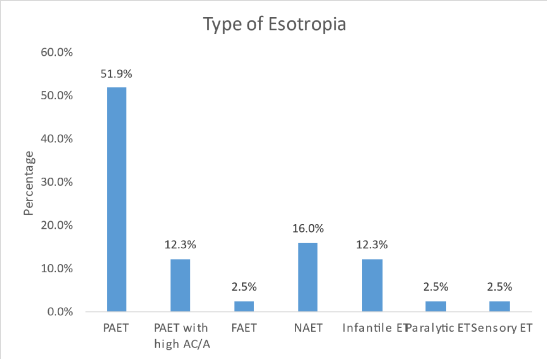

Table 2 lists orthoptic work-up prior to BOTOX injections. About half of the patients (54.3%) had history of amblyopia and quarter of them had inferior oblique overaction (24.7%). One patient had abduction deficit (4th nerve palsy) after head trauma; this patient had papilledema and subdural hematoma. About 58.2% of the patients were on glasses, 11.6% of them had anisometropia. One patient with FAET refused to wear glasses. The most prevalent type of refractive error (Figure 2) was compound hyperopic astigmatism (60.9%) followed by hyperopia (31.9%). Table 3 shows baseline angle of deviation at near and distance with and without correction per type of esotropia. Paralytic and sensory esotropias shows a large angle of deviation; however, the number of patients in these subtypes was low.

Table 2 Orthoptic work-up prior to Botulinum Toxin injections

Parameter	**Level**	**Percentage (count)**
History of amblyopia		54.3% (44/81)

IOOA		24.7% (20/81)
DVD		3.7% (3/81)
Nystagmus		1.2% (1/81)
Abduction deficit		2.5% (2/81)
On glasses		58.2% (69/81)
Anisometropia		11.6% (8/69)
Refractive error	Hyperopia	31.9% (22/69)
	Simple hyperopic astigmatism	0% (0/69)
	Compound hyperopic astigmatism	60.9% (42/69)
	Myopia	0% (0/69)
	Simple myopic astigmatism	1.4% (1/69)
	Compound myopic astigmatism	4.3% (3/69)
	Mixed astigmatism	1.4% (1/69)

IOOA, inferior oblique overaction; DVD, dissociated vertical deviation

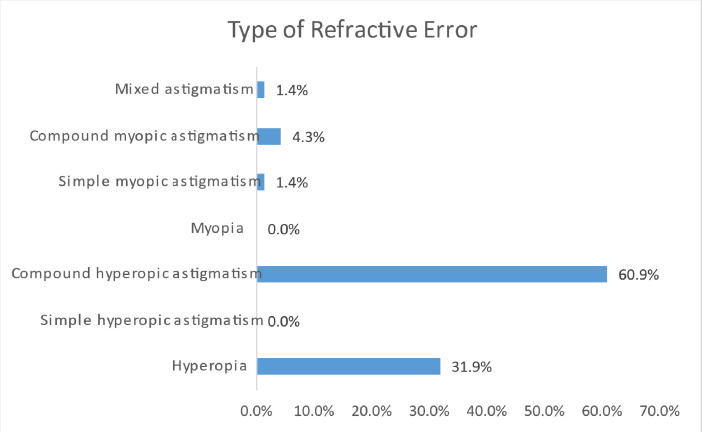

Table 3 Baseline angle of deviation per type of esotropia

Type of Esotropia	Ncc (PD)	Nsc (PD)	Dcc (PD)	Dsc (PD)
PAET	22±7	36±10	19±9	29±8
PAET with high AC/A	18±9	34±9	16±14	24±7
FAET	5±7	23±4	5±7	20±0
NAET	23±7	24±7	15±7	20±5
Infantile ET	29±4	41±6		
Paralytic ET	45	40		
Sensory ET	45	35		

Ncc, angle of deviation at near with correction; Nsc, angle of deviation at near without correction; Dcc, angle of deviation at distance with correction; Dsc, angle of deviation at distance without correction.

Table 4 summarizes the visual acuity, refractive spherical equivalent, and refractive cylinder (astigmatism) in the amblyopic(weak) and sound (strong) eyes. Visual acuity and the refractive error were measured in 75patients and 69patients respectively. The visual acuity in the amblyopic and sound eyes were 20/23 and 20/36 in PAET, 20/24 and 20/32 in PAET with high AC/C ratio, and 20/25 and 20/30 in NAET. The refractive spherical equivalent in the amblyopic and sound eyes was about 3.00D in PAET and 2.00D in PAET with high AC/C ratio, with the later showing higher variability (less homogeneity).

Table 4 Visual Acuity and refractive error per esotropia type prior to Botulinum Toxin injections

ET Type		Visual Acuity (LogMAR)			Refractive Error (D)			
		Amblyopic Eye	Sound Eye		Amblyopic Eye		Sound Eye	
	N			N	SE	Cylinder	SE	Cylinder
PAET	41	0.25±0.32	0.06±0.12	42	3.33±1.58	0.99±0.81	3.03±1.52	0.90±0.76
PAET with high AC/A	10	0.21±0.17	0.08±0.10	10	1.88±3.71	1.05±1.53	2.34±3.36	1.08±1.47
FAET	2	0.05±0.07	0.0±0.0	2	3.00±1.41	0.0±0.0	3.25±1.06	0.0±0.0
NAET	12	0.18±0.22	0.10±0.17	8	1.03±2.72	0.87±0.97	1.11±2.60	0.69±0.84
Infantile ET	7	0.33±0.47	0.29±0.49	5	3.48±1.05	0.75±0.75	2.95±1.15	0.70±0.67
Paralytic ET	2	0.10±0.14	0.10±0.14	1	4.00	0.0	4.00	0.0
Sensory ET	1	5.00	0.0	1	-5.00	2.00	-5.00	2.00
Overall	75	0.30±0.62	0.09±0.19	69	2.74±2.41	0.94±0.95	2.61±2.23	0.85±0.89

SE, spherical equivalent

The refractive cylinder (astigmatism) in the amblyopic and sound eyes was about 1.00D in PAET and PAET with high AC/C ratio, with the later showing higher variability (less homogeneity).

Out of the 81patients, 77.8% (63) received injection only once, 19.8% (16) only twice, and 2.5% (2) trice. Bilateral injection was performed in 97.5% (79), 100% (18), and 100% (2) in the 1st, 2nd, and 3rd injections respectively. The mean dose of BOTOX was 5.49±1.15IU (5.00 to 10.00), 5.42±0.96IU (5.00 to 7.50), and 5.00±0.0IU (5.00 to 5.00) in the 1st, 2nd, and 3rd injections respectively. Tables 5-7 show angle of deviation and complications at per-injections. The mean angle of deviation was similar pre-injections; however, the range was smaller before 2nd and 3rd injections. The majority of patients became small exotropic at first visit then esotropic by the second visit after every injection.

Overall success rate was 38.3% (31). The success rate was 38.1% (16) in PAET, 20% (2) in PAET with high AC/C ratio, 50% (1) in FAET, 76.9% (10) in NAET,100% (2) in paralytic ET, 0% in infantile ET, and 0% in sensory ET. The success rate of 81patients was 29.5% (13) and 48.6% (18) in patients with and without history of amblyopia respectively (p=0.108). The success rate of 69patients was 57.9% (22) and 16.1% (5) in patients with baseline near angle of deviation ≤20PD and >20PD respectively (p<0.001). The success rate of 57patients was 48.3% (14) and 32.1% (9) in patients with baseline distance angle of deviation ≤16PD and >16PD respectively (p=0.166). The success rate of 81patients was 34.1% (14) and 42.5% (17) in patients with and without history of amblyopia respectively (p=0.293).

Table 5 Angle and direction of deviation around 1st Botulinum Toxin injection for 81patients

Time	Level	Mean±SD	Percentage (count)
Prior to 1st injection (PD)			
	Ncc	22±9 (0 to 45)	
	Nsc	34±10 (10 to 55)	
	Dcc	18±10 (0 to 50)	
	Dsc	27±8 (10 to 45)	
First visit post 1st injection			
	Time (week)	2.27±0.91 (0 to 6)	

	Orthotropia		18.5% (15)
	ET		16% (13): small 92.3%(12), moderate 7.7%(1)
	XT		65.4% (53): small 76.9%(40), moderate 7.7%(4), large 15.4%(8)
	Complications		Ptosis 46.9% (38), Pyogenic granuloma 1.2%(1)
Second visit post 1st injection			
	Time (month)	6.36±1.80 (2 to 12)	
	Orthotropia		16% (13)
	ET (PD)	13±9 (0 to 40)	79% (64)
	XT (PD)	7±3 (4 to 10)	4.9% (4)
	Complications		None: 0% (0)
	Motor fusion(<12PD)		69.1% (56)

PD, prism diopter; Ncc, angle of deviation at near with correction; Nsc, angle of deviation at near without correction; Dcc, angle of deviation at distance with correction; Dsc, angle of deviation at distance without correction; ET, esotropia; XT, exotropia.

Table 6 Angle and direction of deviation around 2nd Botulinum Toxin injection for 18patients

Time	**Level**	**Mean±SD**	**Percentage (count)**
Prior to 2nd injection (PD)			
	Ncc	23±8 (14 to 40)	
	Nsc	28±6 (20 to 40)	
	Dcc	18±10 (6 to 40)	
	Dsc	23±6 (18 to 35)	
Time to manifest ET		7.89±2.40 (2 to 12)	
First visit post 2nd injection			
	Orthotropia		22.2% (4)
	ET		11.1% (2): small 100% (2)
	XT		66.7% (12): small 91.7% (11), moderate 8.3% (1)
	Complications		Ptosis 38.9% (7), vertical strabismus 5.6% (1)
Second visit post 2nd injection			
	Orthotropia		16.7% (3)
	ET (PD)	14±9 (6 to 35)	83.3% (15)
	XT (PD)		0% (0)
	Complications		None: 0% (0)

	Motor fusion(<12PD)	62.5% (10/16)

Table 7 Angle and direction of deviation around 3rd Botulinum Toxin injection for 2patients

Time	Level	Mean±SD	Percentage (count)
Time from 2nd to 3rd injection		6±0 (6 to 6)	
Prior to 3rd injection (PD)		28±4 (25 to 30)	
First visit post 3rd injection			
	Orthotropia		0% (0)
	ET		0% (0)
	XT		100% (2): small 50% (1), large 50% (1)
	Complications		vertical strabismus 50% (1)
Second visit post 3rd injection			
	Orthotropia		50% (1)
	ET (PD)	Ncc 16PD Dcc 12PD	50% (1)
	XT (PD)		0% (0)
	Complications		None: 0% (0)
	Motor fusion(<12PD)		50% (1)

Complications:

No eye developed scleral perforation, retinal detachment, nor endophthalmitis. Ptosis was seen at first visit: 46.9% (38/81), 38.9% (7/18), and 0% after 1st, 2nd, and 3rd injections respectively. Pyogenic granuloma 1.2% (1/18) was seen at first visit post 1st injection. Vertical strabismus was seen at first visit: 5.6% (1/18) and 50% (1/2) after 2nd and 3rd injections. None of these mentioned complications were seen by second visit after 1st, 2nd, and 3rd injections. In contrast, consecutive exotropia was present at the first visit in 65.4% (53/81) and 66.7% (12/18) post 1st and 2nd injection respectively; the rate dropped at the second visit post injections to 4.9%(4/81) and 0%(0/18) respectively. Out of the 81patients, 64.2% (52) had no surgery for horizontal strabismus, 28.4% (23) had one surgery, 6.2% (5) had two surgeries, and 1.2% (1) had three surgeries.

Table 8 shows number of surgeries done after BOTOX injections per type of esotropia. Patients who had one or more surgeries were 100% (2/2) sensory ET, 100% (10/10) infantile, 50% (5/10) PAET with high AC/C, and 26.2% (11/42) PAET.

4. Discussion:

Interpretation of the Results:

The study has established that botulinum toxin is an effective treatment for childhood esotropia. The participants in the study were subjected to botulinum toxin injections as a treatment approach to address their esotropia. The results showed that the angle of retraction was well addressed by the use of botulinum toxin treatment with overall success rate of 38.3%(31) with NAET and

paralytic ET scoring the highest success with 76.9%(10) and 100%(2) respectively which defined as a residual angle of deviation of 10 prism diopter (PD) or less which allows for binocularity for at least 6 months. The participants in the study had different angles of deflection with those with mild conditions showing higher success rates. The angle of deviation was measured during the first injection and later during the consecutive injections. It was clear from these measurements that the treatment was effective as the angle grew smaller after every injection. Most of the patients moved from small esotropic after the first injection to esotropic during the second injection. Such transformation attests to the effectiveness of botulinum toxin as a treatment option for childhood esotropia. The participants who underwent the treatment experienced few complications, which is an indication of the effectiveness of the approach. The results also show that the use of botulinum toxin is not effective in all cases. There are some patients who did not respond well particularly infantile(8) and sensory(1) ET showed no improvement at all to botulinum toxin and had to be referred for surgical operation. As a result, it can be concluded that botulinum toxin is effective in most instances but it should be used alongside surgery for those patients who do not respond well to the treatment.

Implications of the Study:

The study has shown the effectiveness of botulinum toxin in treating childhood esotropia to be very high. As such, it can be used as an alternative to surgery which has for a long time been considered to be the most effective treatment method for childhood esotropia. With the findings from this study, two things are clear. First, botulinum toxin treatment is a safe medical practice which can be carried out to treat esotropia in children. Second, the study has shown that the treatment is as effective as surgery and has few side effects with minor complications most commonly ptosis by 46.9% after first dose and 38.9% after 2nd which resolved after 2nd injection follow up, However there was no visual loss or major complication(scleral perforation, retinal detachment, or endophthalmitis) in any case. In addition, botulinum toxin treatment is less invasive as compared to surgery. Surgery also poses the threat of re-operation making it a more invasive procedure. The study has also shown that the method can be effective even with patients with higher angle of deviation. Most of the cases that have traditionally been treated using botulinum toxin treatment happen when the patient has small angle of deviation and the outcomes were very successful. Traditionally, patients who had higher angle of deviation were scheduled for surgery as it was deemed to be more effective. With the use of higher dosage, it is now possible to treat patients with large angles of deviation. However, there are some instances where the patient does not respond well to botulinum toxin treatment and surgery is recommended in such cases. In the study, patients whose angle of deviation was more than 20 after the initial dosage were advised to undergo surgery as they were determined not to be responding well to botulinum toxin treatment.

Limitations:

The generalizability of the results is limited by the low number of subjects in the research. Notably, only 116 patients were included in the study. Moreover, the methodological choice was constrained to just patients who received their botulinum toxin injections in King Fahad Armed Force Hospital (KFAFH), Jeddah, Saudi Arabia for a period of 5 years. As such, it is difficult to generalize the results of this study to the general population and patients treated in other healthcare facilities or regions. During the study, there were some confounding variables that the researcher was unable to control. For instance, some caregivers were unwilling to have their patients take the second dose, instead preferring surgical intervention. Although the researcher would, therefore, explain the pros and cons of each procedure then proceed to offer the treatment option chosen by the caregiver. Ultimately, this reduced the amount of data available for analysis and generalization on the impact and effectiveness of the second dose. Nonetheless, the results of the study are still valid in analyzing

the indications, effectiveness and side effects of Botulinum toxin in the management of Childhood Esotropia as the study was scientific, had strict exclusion criteria, and the patients received pre and post-injection follow-up.

Study Recommendations:

Future studies should take into account patients who receive botulinum toxin injections outside KFAF as this will increase the target population, hence offer broader and more reliable results. The sample size can also be increased to give room for statistical comparison and reduce margin of error. Lastly, further study can encompass the period between 2020 – 2021 to determine the impact of COVID-19 on the indications, effectiveness and side effects of Botulinum toxin in the management of Childhood Esotropia.

5. Conclusion:

Botulinum toxin represents a safe, repeatable alternative to surgery in the management of esotropia type of strabismus. Success rate differs in different diagnoses with NAET scoring the highest. In our study, we couldn't find definitive factors affecting the success rate. Further large scale, prospective studies are needed.

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