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The Incidence, Clinical features, and Management of Essential Infantile Esotropia in the United Kingdom. A British Ophthalmology Surveillance Unit (BOSU) study

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Abstract

Background/Objectives

A national study was undertaken through the British ophthalmology surveillance unit (BOSU) to determine the incidence presenting features and management of essential infantile esotropia (EIE) in the UK

Methods

Data from a prospective national observational study of newly diagnosed EIE presenting to clinicians in the United Kingdom over a 12-month period was collected. Cases with a confirmed diagnosis by a clinician of a constant, non-accommodative esotropia ≥ 20 prism dioptres (PD), presenting at ≤ 12months, with no neurological or ocular abnormalities were identified through BOSU. Follow up data was collected at 12 months.

Results

A total of 57 cases were reported giving an incidence of EIE of 1 in 12,828 live births. The mean age of diagnosis and intervention were 7.05±2.6 months (range 2-12) and 14.7±4.9 months(range 6.5-28.1) respectively. Management was surgical in 59.6%, botulinum toxin alone in 22.8%, and 17.5% were observed. The preoperative angle of esotropia was smaller in the observation group (P=0.04). The post-operative angle of esotropia was not statistically significant between botulinum toxin or surgery (P=0.3) though the age of intervention was earlier in the botulinum group (P=0.007). Early intervention (before 12 months of age) did not influence the post intervention motor outcomes between 0-10 prism dioptres of esotropia (P=0.78).

Conclusions

The incidence of EIE in the UK is considerably lower than reported in other population-based studies. The preferred method of treatment was surgical with earlier intervention in those treated with botulinum toxin. An early age of intervention did not influence motor outcomes.

Introduction

Retrospective reviews of medical records with a diagnosis of essential infantile esotropia (EIE) over a 30-year period report a birth prevalence of 25/10 000 population in the USA (1). Neither the incidence or the surgical rates of EIE over this period, changed in this population. A number of studies from the UK report a 42% to 58% decline in the surgical procedures for childhood esotropia (2-5). While one study reported a 55% decrease in strabismus referrals in children under 14 years over a 20 year period (3), a study from Scotland suggested a stable prevalence over a 10 year period but decreased surgical rates (5). Data was presented which showed full cycloplegic refractive correction in these children may explain the decline in squint surgery rates. In addition, better childhood surveillance programmes that allow an early diagnosis and prompt correction of refractive errors and amblyopia (4, 5), a declining incidence and better children health outcomes have been put forward as reasons for this decline (3, 6). A more recent study from the UK to assess whether the trend for declining surgery continued suggested a further decline till the year 2006 and stabilised surgical rates from then onwards (7).

The studies from the UK looked at all childhood esotropia and not EIE in isolation and while early refractive correction and amblyopia management of accommodative or partially accommodative esotropia may reduce surgical rates this should not affect children with EIE. Extrapolating the EIE prevalence of 1 in every 403 live births from a population study in the

USA (1) to the rate of live births in the UK would suggest that the numbers of EIE cases per year does not mirror the experience of clinicians in the UK.

The timing of intervention and the type of intervention continues to be debated (8, 9). Early alignment of the visual axis with surgery or botulinum toxin has been associated with superior binocular outcomes (10-13). Comparative studies suggested better motor outcomes with surgery (14, 15). The arguments for early surgery in EIE to promote superior motor and sensory outcomes is well articulated in scientific literature. How early to intervene will depend on the stability of the deviation and the age of presentation (16). The early surgical alignment in EIE has been reported as unstable in 46% (17) with a high reoperation rate of 60 to 80% (18). Other studies however argue a higher rate of binocular outcomes with early surgery and similar reoperation rates for early or later surgical correction (19).

The previous studies on the prevalence date in EIE has been retrospective. We undertook a prospective surveillance study with the British Ophthalmic Surveillance Unit over a 12 month to establish the incidence of EIE in the UK and the clinical presentation and practice patterns of management.

Material and Methods

This was a prospective observational study of incident cases of essential infantile esotropia presenting between September 2017 and October 2018 within the UK. All infants less than 12 months of age diagnosed by a clinician (orthoptist or ophthalmologist) with EIE were included. The case definition of EIE was a non-accommodative esotropia greater or equal to 20 prism dioptres diagnosed before the age of 12 months, with a stable angle of esotropia,

in the absence of a neurological disorder. Crucially cases presenting or examined by a clinician later than 12 months of age were excluded regardless of a parental history suggesting an earlier onset.

Incident cases were ascertained every month through the British Ophthalmological Surveillance Unit (BOSU) reporting card system. An initial questionnaire was then sent to the reporting ophthalmologist along with a follow up questionnaire at a 6-month interval. The questionnaires were designed in conjunction with the British Ophthalmological Surveillance Unit (BOSU) committee. Ethical approval was obtained through the National Research Ethics Society in the UK.

The initial questionnaire collected demographic data on age, gender, prematurity, visual acuity, angle of deviation, cycloplegic refraction, ocular motility examination, treatment plan and follow up. The details collected in a follow up questionnaire were details of management with either observation, botulinum toxin, surgery and the outcomes. Additionally, the presence of latent or manifest nystagmus, dissociated vertical deviation and inferior oblique overaction were requested.

Descriptive statistical methods of mean, standard deviations and range are reported. Comparative analysis of means of continuous variables to identify differences between the methods of intervention or observation used ANOVA (analysis of variance). For categorical data cross tabulation tables with counts and percentages used the Chi square test to identify differences between the groups. SPSS 25(IBM Corp. Released 2017. IBM SPSS Statistics

for Windows, Version 25.0. Armonk, NY: IBM Corp.) was used for this analysis

Results

There were 67 returns of both initial and follow up questionnaires. There were 10 that were excluded as 6 did not meet inclusion criteria (3 had neurological problems reported on follow up. In 3 cases the diagnosis changed to an accommodative esotropia, a nerve palsy and nystagmus blockage syndrome); 2 were duplicates, 1 was the wrong patient identity and 1 follow up data was not returned. This left a total of 57 infants with EIE diagnosed in the first 12 months of life that were included in the study. This gives an annual incidence of 1 in 12,828 live births. From previous BOSU studies it is estimated that there is an average of 30% of cases underreported. Extrapolating the average underreporting to this study the corrected estimated annual incidence would be 1 in 9027 live births.

The average age at diagnosis was 7.05±2.6 months with a range of 2 to 12 months. The average age of onset, as reported by the parents/carer, was 1.41±1.9 months with a range of 0 to 7 months. There were 52.7% (30 cases) female cases, 86.5% (45 cases) were Caucasian, 5.8% Arabic, 3.8% Afro-Caribbean and 3.8% Asian. Prematurity between 32 to 37 weeks were seen in 32.1%.

There were 10.5% with systemic disease; 3 with mild developmental delay, 1 with liver failure and 2 with a history of seizures. Over elevation in adduction (OEIA) or inferior oblique overaction was present in 25 infants on follow up (43.9%), dissociated vertical deviation in one patient (1.8%) and latent nystagmus in 3 (5.3%) children. The average angle

of deviation was 42.1 ±9.2 prism dioptres (PD) with a range of 25 to 65 dioptres. The mean angle of deviation at last follow-up after surgery or botulinum toxin injections was 12.2 ±4.1 prism dioptres range (-30 to 40 dioptres). The mean refractive error was +2.2 ± 1.4 dioptres (spherical equivalent). The mean duration of follow up was 13.0± 6.6 months (range 0.5 to 30.01 months). There were 5 missing entries for ethnicity and 1 missing entry for birth history (Table 1). Of the 57 cases, 34 had surgery, 13 had botulinum toxin and 10 were observed (Table 2).

Surgically treated group

The surgical group had 76.4% bilateral symmetrical surgery (bilateral medial rectus recessions) and 23.6% had unilateral surgery (medial rectus recession and lateral rectus resection). The majority of recessions (60%) were using a modified hang back technique from the original insertion with a small scleral bite at the intended measured recession site, with an equal number of recessions (20%) using a fixed scleral bite at the intended measured recession site or a hang back of the measured amount from the insertion without a bite at the intended site of recession. Three patients in the surgical group had surgery augmented with botulinum toxin injections at the time of surgery (2.5 units in both medial recti and 1 patient received 3.75 units in both medial recti at the time of surgery). The mean age at diagnosis in the surgical group was 7.3±2.7 months and the age at the time of surgery was 15.9±5 months. The mean preoperative and postoperative angle in the surgical group was 44.9±8.6 PD and 10.7±15.1 PD respectively. Postoperatively at final follow up there were 45.4% (15 cases) within 10 PD, 24.2% (8 cases) between 11 to 20 PD, 12.1% (4 cases) between 21 to 30 PD, 9% (3 cases) between 31 to 40 PD of esotropia and 3 cases (9%) with over-corrections of 5PD, 25PD and 30PD of exotropia (1 missing value). The latter one was re-operated with re-

advancement of both the recessed medial recti. The average follow up in this group was 12.13±6.8 months. There were 32.3% (11 children) who received treatment for amblyopia, 41.2% (14 children) with OEIA, 2.9% with DVD and 2.9% with nystagmus.

Botulinum toxin treated group

The botulinum toxin alone group had one injection to both medial rectus muscles in 11 patients and 2 patients had a repeat injection. The number of units injected were between 1 to 2.5 units (2 cases received dysport -botulinum toxin A (Ipsen Ltd Berkshire UK) of 2.5 units each eye and 2 patients received botox Allergan-botulinum toxin A (Teleta Ltd- Glasgow UK) of 2.5 units each eye; the brand name was not mentioned in the others). The mean age of diagnosis in the botulinum toxin group was 6.4±2.9 months. The age at the time of injection was 11.6±3.3 months which was statistically significant (P=0.007) when compared to the age at the time of surgery. The mean pre-injections and post-injection angle was 42.3±9.9 PD and 16±9.3 PD respectively. Postoperatively at final follow up there were 30% (3 cases) within 10 PD, 50% (5 cases) between 11 to 20 PD, 20% (2 cases) between 21 to 30 PD, 9 % (3 cases) between 31 to 40 PD of esotropia and there were no over-corrections (3 missing values). Though there were fewer within 10 PD of esotropia in the botulinum group this was not statistically significant (p=0.6) which may be due to small numbers. Transient ptosis was reported in 23% of children (3 cases) who received botulinum toxin injections. The average follow-up in this group was 14.5±6.6 months. There were 15.4% (2 cases) who received treatment for amblyopia, 38.5% (5 cases) with OEIA and none with DVD or nystagmus noted in follow up.

Observation group

In the observation group the mean age at the time of diagnosis was 7.14±2.4 months with a mean angle of esotropia of 35±7.9 PD. The mean duration of follow up was 15.4±6.5 months. In this group 70% (7 cases) were treated for amblyopia, 60% (6 cases) had OEIA, none had DVD and 20% (2 cases) had latent nystagmus. The reason for non-intervention is this group were parental choice in 3 cases, 2 of whom were receiving treatment for amblyopia and in the other case the parent requested surgery at 24 months of age. In one case the clinician mentioned 24 to 48 months for surgery was usual practice. In the other cases on going treatment for amblyopia was reported as reasons for non-intervention.

Comparative analysis

There was no significant difference in the age of presentation (P=0.6), gender (P=0.8), prematurity (P=0.5), deprivation indices (P=0.68), refraction (P=0.7), OEIA (P=0.6), DVD (P=0.7) or follow up (P=0.3) between the three groups. The angle of esotropia was smaller in the observation group (P=0.04) (Figure 1). The post-operative angle of esotropia was not statistically significant between botulinum toxin or surgery (P=0.3). The age of intervention was earlier in the botulinum group (P=0.007)(Figure 2). The age of intervention in both surgical and botulinum toxin group did seem to influence the motor outcomes. To explore this the age of intervention was grouped into those infants who had an intervention at 12 months or less and those over 12 months at the time of intervention. There was no statistical difference in those operated at 12 months or less and those over 12 months in achieving a post intervention angle at final follow up of 0 to 10 PD or greater than 10 PD (P= 0.78). Similarly comparing the intervention groups independently using the same age groups for

comparison of early and later intervention there was no statistical difference in the motor outcomes between the surgical and botulinum toxin groups (P=0.47)

Amblyopia (P=0.02) and latent nystagmus (P=0.009) was more common in the observation group.

Discussion

This prospective surveillance study has reported a corrected incidence of 1 in 9027 live births in the UK. All included children had a diagnosis confirmed by a clinician of a constant, non-accommodative esotropia ≥20 PD by the age of 12 months. There were 59.6% treated surgically, 22.8% with botulinum toxin injections and 17.5% were observed. There was no significant difference in the age of diagnosis in the surgical, injection and observation groups. There was a slightly younger age of injections compared to surgery 11.6 months vs 15.9 months. The mean postoperative angle was lower in the surgical group compared to the injection group (10.7PD vs 16PD) though this was not statistically significant. Though not statistically significant children with a final angle of ≤10PD of esotropia was higher in the surgical group (45.9% vs 30%.). Amblyopia and nystagmus were common in the observation group. Overcorrections were only seen in the surgical group. The length of follow up was similar for all. This study presents the management practice of EIE in the UK.

An early epidemiological study in 1974 of strabismus in a defined birth cohort examined at school age reported a high prevalence of 10.2 cases of non-accommodative esotropia per 1000 population (20). This study however had no definition of EIE and earliest age of

diagnosis was 21 months. It is likely that this study included what is currently defined as EIE and all non-accommodative esotropia in children at school age. A more recent study from the USA in a defined population reported a prevalence of EIE of 1 in 403 live births (1). Though this study included a definition of EIE its inclusion criteria did not mandate for a clinical confirmed diagnosis before the age of 12 months. In addition, it included all cases over a 30-year period where a strict diagnosis of EIE may have included infants born with extreme prematurity which was excluded in our cohort (< 32 weeks gestational age) due to the high prevalence of esotropia in this group of infants (21, 22). Hence it is not possible to extrapolate from our results that the incidence is decreasing as the studies are not comparable in terms of cases included. In addition, this is the first prospective study of EIE in the UK. We acknowledge the low incidence in our study may be partly due to under reporting of our work and the fact that some children with all the signs of EIE may present or are referred late to the clinical services.

The mean age of presentation accepting a historical diagnosis of other studies is similar to our study (23). However, a historical diagnosis of esotropia by parents or carers is subject to inaccuracies of lay observation. Esotropia observed by parents may be intermittent and variable (17) often resolving by 12 months of age (24). A constant large angle esotropia is unlikely to spontaneously resolve (25) hence we chose to include only infants who had a clinically confirmed constant esotropia ≥ 20 PD.

Though the age of intervention varied between 6.5 months to 28 months this did not affect a successful motor outcome between 0 to 10 PD of esotropia. Studies have reported superior sensory outcomes with early intervention Wright et al who operated on 7 patients between 13

and 19 weeks of age (11) and Birch et al who operated on 50 children before 6 months of age (19) . At the same time, there are reports of a higher reoperation rate with early surgery for example in the ELISSS study (where early was defined as 6-24 months of age) (13, 18). Earlier age of intervention in our study was not related to the age at diagnosis, hence the age of intervention may reflect the practice of surgeons, the parental choice of age of intervention or the need to treat amblyopia prior to intervention as evidenced by the observation group with a higher proportion of amblyopia than the intervention groups.

We defined early intervention as under 12 months of age rather than 24 months as the study period ran for 12 months (BOSU studies looks for incidence of disease) with a follow up questionnaire sent 12 months after the initial reporting. In addition only cases which were clinically diagnosed less than 12 months of age which meant they were true new cases only. A child presenting at age 2 for the first time ever would have been excluded even if the parental reported onset was less than 12 months of age.

This meant that we captured a very young group and naturally that meant that if they were to receive an intervention it would have been done less than 24 months of age.

There is also no specific consensus on the definition of "early". A recent systematic review (26) outlined the prospective studies done since 2000. These were the following definitions of what constitutes as the early interventional period in the 5 studies that looked at timing of surgery.

The average age at diagnosis in our group was 7.05±2.6 months with a range of 2-12 months. The average age of onset however, as reported by the parents/carer, was 1.41±1.9 with a range of 0-7 months. Our study supports the fact that recruiting patients for a hypothetical

early intervention (within the first few months of the misalignment) would be challenging. Therefore, 12 months of age as the cut off is potentially a more realistic target to work off on.

The choice of the type of intervention with botulinum toxin or surgery reflected surgeon practice as there was no relationship between age of diagnosis and choice of intervention. The results favour slightly better motor outcomes in the surgical group though this was not statistically significant. All the overcorrections were in the surgical group and none in the botulinum toxin group. Recent studies report better motor outcomes for large angle esotropia with surgery compared to botulinum toxin injections, however the age of inclusion in these studies ranged from 6 months to 6 years. There was no statistically significant difference in our study between the surgical group and the botulinum toxin group in those achieving 0 to 10 PD of esotropia. However, this needs to be interpreted with caution due to the small sample size.

This data provides evidence that early intervention under 12 months of age does not necessarily guarantee superior motor outcomes when compared to interventions done from 12-28 months of age. This appears to be true regardless of the type of intervention.

This is the first prospective observational study in the UK reporting on the incidence, presentation, and management of children with EIE. It reflects the current practice of surgeons in the UK. It provides a benchmark for further studies on EIE. The limitation of this study are the small sample size and the possibility of significant under reporting. Within the limitations of an observation surveillance study however it provides evidence that early intervention does not guarantee superior motor outcomes.

Further studies on the longer-term outcome will provide an evidence base for decision making on the timing and type of intervention within the context of parental choice.

Conclusions

Despite the possibility of under reporting our studies report a lower incidence of EIE in the UK compared to population studies elsewhere. Surgical intervention is preferred over botulinum toxin injections. Age and type of intervention did not influence motor outcomes. A significant proportion of infants were observed due to parental choice, although the presence of amblyopia and a smaller angle could have influenced this.

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Figure 1: Box plots of pre- intervention angle

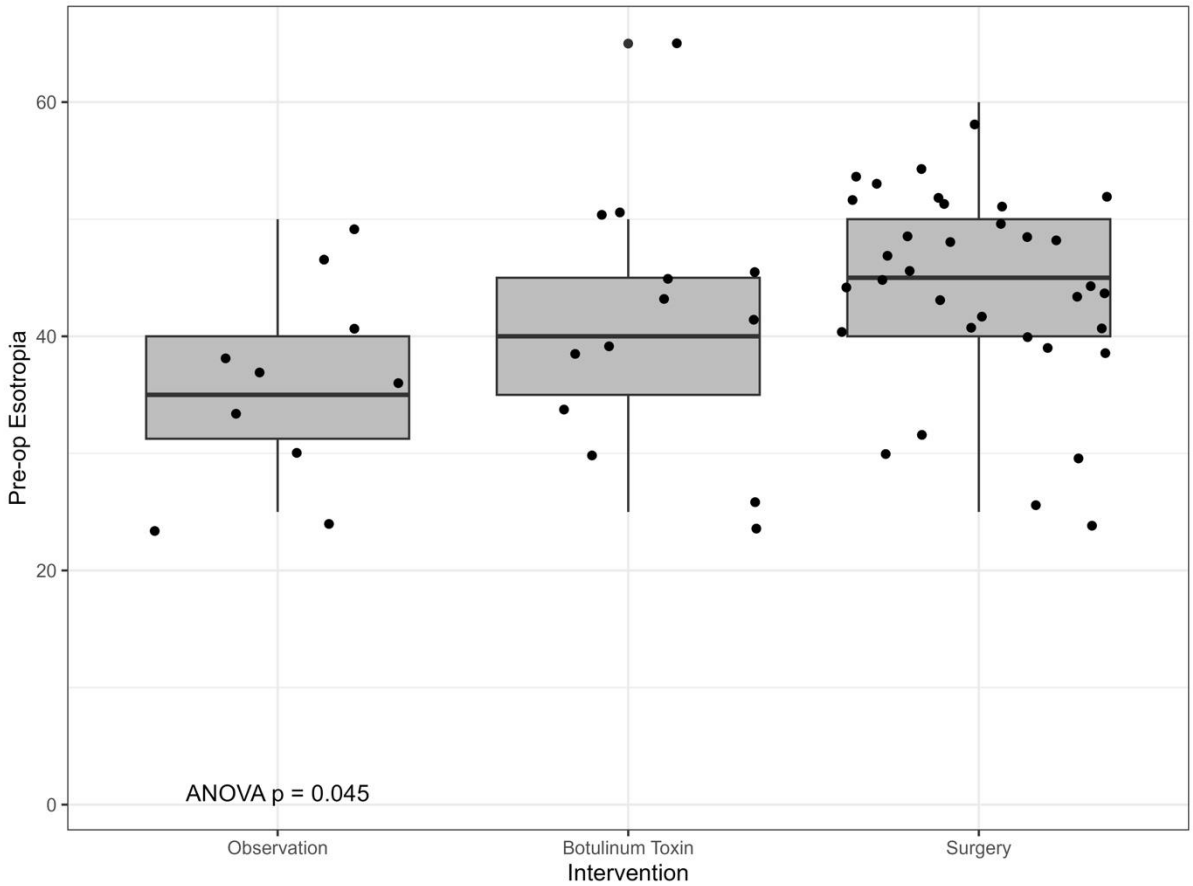

Figure 2: Age of intervention

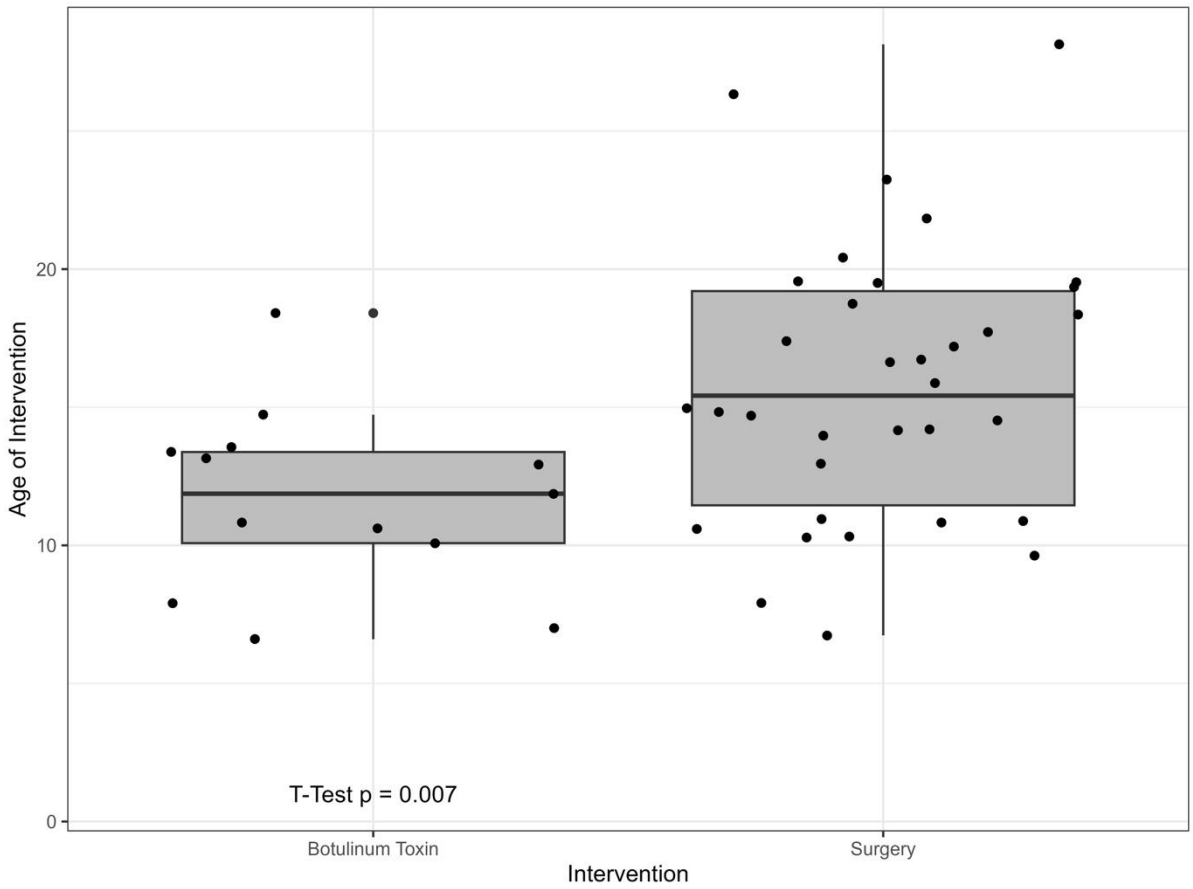

Table 1: Demographics, clinical presentation and follow up of children with Essential Infantile Esotropia (EIE).

EIE with complete follow up -n= 57				
	Mean (SD)		Median	Range
Age at diagnosis (months)	7.05(2.6)		7	2 to 12
Age at botulinum toxin or surgery (months)	14.7(4.9)		14.2	6.5 to 28.1
Esotropia (PD) at diagnosis	42.1(9.2)		45	25 to 65
Esotropia (PD) Post- surgery or botulinum toxin	12.2(14.1.)		12	-30 to 40
Follow up (months)	13.01(6.6)		13.94	0.5 to 30.01
Refraction -right (dioptres)	+2.2 (1.4)		+2.25	-1 to +5.3
Refraction- left (dioptres)	+2.3 (1.4)		+2.5	-0.25 to +5
Gender	Female (n)		Male (n)	
	52.7% (30)		47.3% (27)	
Ethnicity*	Afro-Caribbean (n)	Arabic (n)	Asian(n)	Caucasian(n)
	3.8% (2)	5.8% (3)	3.8% (2)	86.5% (45)
Birth History*	Prematurity (n) (32-37 weeks)		Term (n) (>37 weeks)	
	32.1% (18)		67.9% (38)	
Systemic diseases (n)	10.5% (6)	Mild developmental delay 3 Liver failure 1, Seizures 2		
Amblyopia treatment (n)	35.1% (20)			
IO o/a, or OEIA (n)	43.9% (25)			
DVD (n)	1.8% (1)			
Latent nystagmus (n)	5.3% (3)			
Legend: n= number, PD= prism dioptres, IO= inferior oblique, o/a = over action, OEIA= over elevation in adduction, DVD= dissociated vertical deviation, EIE= essential infantile esotropia, * missing entries for ethnicity and birth history				

399 Table 2: Comparison between Surgical group, Botulinum group and Observation group

	Surgical			Botulinum toxin			Observation		
Number	59.6% (n=34)			22.8% (n=13)			17.5% (n=10)		
Gender	female		male	female		male	female		male
	50% (n=17)		50% (n=17)	53.7% (n=7)		46.2% (n=6)	70% (n=7)		30% (n=3)
	Mean (SD)	median	range	Mean (SD)	median	range	Mean (SD)	median	range
Age at diagnosis (months)	7.3(2.7)	7.1	2 to 12	6.4(2.9)	6	3 to 12	7.14(2.4)	7	3 to 11
Age at intervention (months)	15.9(5)	15.4	6.7 to 28.1	11.6(3.3)	11.9	6.5 to 18.4	-	-	-
Esotropia (PD)- pre op	44.9(8.6)	45	25 to 60	42.3(9.9)	40	25 to 65	35(7.9)	35	25 to 50
Esotropia (PD)- post op	10.7(15.1)	10	-30 to 40	16(9.3)	20	0 to 25	-	-	-
Change in angle of esotropia (PD)	31.2(15.6)	33	5 to 55	23(7.2)	20	15 to 30	-	-	-
Follow up (months)	12.13(6.8)	11.8	2 weeks to 25 months	14.5(6.6)	16.2	3 weeks to 21.5 months	15.4(6.5)	14.7	8.3 to 30.01 months
Refraction - R	+2.1(1.2)	2.4	-1 to +4.75	2.4(1.6)	2.5	+0.125 to +5.3	1.9(1.5)	2	-0.5 to +3.75
Refraction - L	+2.3(1.2)	2.5	-0.25 to +4.75	2.5(1.5)	2.3	+0.5 to +4.5	1.8(1.5)	1.8	-0.5 to +3.75
Amblyopia treatment	32.3% (11)			15.4% (2)			70% (7)		
IO o/a, or OEIA	41.2% (14)			38.5% (5)			60% (6)		
DVD	2.9% (1)			0			0		
Nystagmus	2.9% (1)			0			20% (2)		
Legend: n= number, PD= prism dioptres, R= Right, L= Left, IO= inferior oblique, o/a over action, OEIA over elevation in adduction, DVD= dissociated vertical deviation.									

400

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