

# Different surgical outcomes in infantile exotropia according to onset time



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## PURPOSE

To determine whether age of onset influences surgical outcomes in infantile exotropia.

## METHODS

The medical records of patients at our tertiary care facility who underwent bilateral lateral rectus recession for infantile exotropia during the period 2004–2013 were reviewed retrospectively. Patients were grouped by onset age: 6 months or earlier (E6 group) or later than 6 months (L6 group). Motor outcomes, near stereoacuity, and distance fusional status in both groups were evaluated.

## RESULTS

A total of 134 patients were included: 35 in the E6 group and 99 in the L6 group. At a mean follow-up of 4.6 years, recurrence occurred in 12 (34%) of the E6 group and 38 (38%) of the L6 group ( $P = 0.496$ ). Overcorrection occurred in 3 (9%) of the E6 group and in 4 (4%) of the L6 group ( $P = 0.341$ ). In the analysis of 109 patients eligible for sensory examinations, the E6 group demonstrated a higher proportion of patients with reduced stereoacuity of 80 arcsec or worse (54% vs 25% [ $P = 0.007$ ]) and suppression (46% vs 12% [ $P < 0.001$ ]) compared with those in the L6 group. In logistic regression analyses, onset of  $\leq 6$  months was significantly associated with reduced stereoacuity (OR = 6.42) and suppression (OR = 37.67) but not with recurrence or overcorrection.

## CONCLUSIONS

In our study cohort, age of onset  $\leq 6$  months was associated with worse sensory prognosis for children with infantile exotropia but not with a difference in motor outcomes. (J AAPOS 2019;23:317.e1-6)

Infantile exotropia in a healthy child  $< 1$  year of age is rare. Research on infantile exotropia has been limited. Hiles and Biglan coined the term *infantile exotropia* in their 1983 study of patients who had early-onset exotropia ( $< 1$  year of age) and were operated on before 2 years of age.<sup>1</sup> Costenbader<sup>2</sup> originally reserved the term *congenital esotropia* for infants with large-angle esotropia documented in the first 6 months of life and used *infantile esotropia* to describe a more heterogeneous population of patients with any esotropia presenting in the first year of life. When exotropia presents during the first year of life, both terms have been used to describe patients with large-angle deviations presenting in either the first 6 months or the first year of life with a stable angle and normal central nervous system.<sup>2,3</sup>

Because ocular misalignment in the early period of life can exert a negative influence on binocular sensory function,<sup>4</sup> it is possible that surgical prognosis of infantile exo-

tropia is affected by age of onset. To our knowledge, however, previous studies on infantile exotropia have not addressed this. The purpose of the present study was to determine whether exotropia occurring before or after 6 months of life influenced surgical outcomes in patients with infantile exotropia.

## Subjects and Methods

This study was approved by the Institutional Review Board of Korea University Medical Center and adhered to the tenets of the Declaration of Helsinki. The medical records of all exotropia patients with reported onset by 12 months of age operated on at Korea University Medical Center from January 1, 2004, to December 31, 2013 were reviewed retrospectively. Patients with postoperative follow-up of  $< 2$  years were excluded. Patients with anterior segment or retinal abnormalities, disorders of the central nervous system, craniofacial anomalies, or genetic diseases were also excluded.

Patients were divided into two groups according to age of exotropia onset:  $\leq 6$  months of age (E6 group) or  $> 6$  months (L6 group). To determine age onset, parents or guardians were asked when they first noticed an exodeviation in their children. Reported onset of exotropia was confirmed by photographic evidence for all patients.<sup>3,5-7</sup>

The following evaluations were performed the day before surgery: measurement of deviation angles by prism and alternate cover test at distance (6 m) and near (1/3 m) fixation; motor functions, including ductions and versions, presence of dissociated vertical deviation and overelevation in adduction; constancy of

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Table 1. Surgical dosage in bilateral lateral rectus recession

Deviation, PD	Recession, mm	
	Conventional	Reduced
20	5	5/4 or 4/4
25	6	6/5 or 5/5
30	7	7/6 or 6/6
35	7.5	7/7 or 7/6
40	8	8/7 or 7/7

PD, prism diopter.

deviation; measurement of refractive errors; and fundus examination. Duration of exotropia was defined as the time from the onset to surgery. Refractive errors were measured by cycloplegic refraction and evaluated as spherical equivalents. Anisometropia was defined as a difference in spherical equivalent between the two eyes  $\geq 1.50$  D.

Surgery was performed when exodeviation was at least 20<sup>A</sup>, with a stable measurement of deviation angles over at least three consecutive visits. Bilateral lateral rectus muscle recession was performed for all patients under general anesthesia by the same surgeon (SHK). The surgical dose was either the conventional one (according to the Wright's table<sup>8</sup>) or the conventional amount reduced by 1–2 mm (Table 1). An inferotemporal fornix incision was used for all surgical procedures.

Postoperative alignment in primary position was assessed postoperatively on 1 day and at 1 week, 1, 3, 6, 12, and 24 months, and every 6 months thereafter. Recurrence was defined as exodeviation of  $>8^{\Delta}$ ; overcorrection, as esodeviation of  $>5^{\Delta}$ . Sensory outcomes were evaluated using the Titmus stereo test (Stereo Optical Co. Chicago, IL) for near stereoacuity and Vectogram (Luneau L29 chart projector; Luneau SAS, Chartres, France) for sensory fusion at distance. Presence of amblyopia, defined as interocular difference of 2 lines of visual acuity, was also assessed postoperatively.

Baseline characteristics and motor/sensory outcomes were compared between groups. The independent *t* test was used to compare continuous variables. Associations between categorical variables were assessed using the  $\chi^2$  test or the Fisher exact test. Rates of recurrence and overcorrection were compared with log-rank test based on Kaplan-Meier analysis. Results of the Titmus stereo test were evaluated based on the best value measured after age 5. In this study, the degree of near stereoacuity was classified as either fine or reduced. A fine stereoacuity was defined as 60 arcsec or better, which could be regarded as bifixation status<sup>9,10</sup>; reduced stereoacuity was defined as 80 arcsec or worse. Distant fusional status was assessed at the time of the best stereoacuity and classified as either fusion or suppression.

Logistic regression analysis was performed to determine the odds of exotropia onset of  $\leq 6$  months for recurrence, overcorrection, reduced stereoacuity, and suppression. Variables for analyses of recurrence and overcorrection included sex, duration of exotropia, preoperative deviation, constant deviation, dissociated vertical deviation, overelevation in adduction, refractive errors, anisometropia, type of surgery, and amblyopia. For stereoacuity and suppression, age and deviation angles at time of sensory examination were incorporated into the regression model. Odds ra-

Table 2. Characteristics of patients with infantile exotropia grouped by exotropia onset time

Characteristic	E6 group (n = 35) <sup>a</sup>	L6 group (n = 99) <sup>a</sup>	P value
Female sex, no. (%)	19 (54.3)	64 (64.6)	0.278 <sup>b</sup>
Duration of exotropia, months	43.1 $\pm$ 35.1	28.6 $\pm$ 17.6	0.024 <sup>c</sup>
Time interval between first visit and surgery, months	8.2 $\pm$ 14.7	4.8 $\pm$ 7.3	0.193 <sup>c</sup>
Preoperative deviation, PD	30.7 $\pm$ 5.2	30.4 $\pm$ 4.4	0.689 <sup>c</sup>
Constant deviation, no. (%)	21 (60.0)	40 (40.4)	0.045 <sup>a</sup>
Associated features			
DVD, no. (%)	3 (8.6)	13 (13.1)	0.561 <sup>d</sup>
Overelevation in adduction, no. (%)	8 (22.9)	21 (21.2)	0.839 <sup>b</sup>
Refractive errors, D	-0.2 $\pm$ 1.5	-0.1 $\pm$ 1.2	0.684 <sup>c</sup>
Anisometropia, no. (%)	3 (8.6)	6 (6.1)	0.696 <sup>d</sup>
Age at surgery, months	45.5 $\pm$ 33.7	39.7 $\pm$ 17.8	0.338 <sup>c</sup>
Surgical method			
Conventional recession	22 (62.9)	49 (49.5)	0.173 <sup>b</sup>
Reduced recession	13 (37.1)	50 (50.5)	
Follow-up duration, months	58.5 $\pm$ 30.7	53.5 $\pm$ 25.5	0.348 <sup>c</sup>

D, diopter; DVD, dissociated vertical deviation; E6 group, patients with infantile exotropia that occurred by 6 months of age; L6 group, patients with infantile exotropia that occurred later than 6 months of age; PD, prism diopter.

<sup>a</sup>Continuous variables are reported as mean  $\pm$  standard deviation.

<sup>b</sup> $\chi^2$  test.

<sup>c</sup>Independent *t* test.

<sup>d</sup>Fisher exact test.

tios and their 95% confidence intervals were calculated. A *P* value of  $< 0.05$  was considered statistically significant. Statistical analyses were conducted using SPSS for Windows (V.21.0; SPSS Inc, Chicago, IL).

## Results

Of the 159 patients who were initially enrolled in this study, 25 did not meet inclusion criteria. A total of 134 patients were included: 35 in the E6 group and 99 in the L6 group.

Mean age at onset was 2.4 months in the E6 group and 11.1 months in the L6 group ( $P < 0.001$ ). The average duration of exodeviation in the E6 group was 43.1 months; in the L6 group, 28.6 months ( $P = 0.024$ ). On preoperative examination, the proportion of patients demonstrating

Table 3. Surgical outcomes in the two groups of infantile exotropia according to onset time

Surgical outcome	E6 group	L6 group	P value
<b>Motor outcome</b> (n = 134), no. (%)			
Recurrence	12/35 (34.3)	38/99 (38.4)	0.496 <sup>a</sup>
Overcorrection	3/35 (8.6)	4/99 (4.0)	0.341 <sup>a</sup>
<b>Sensory outcome</b> (n = 109)			
Age, months, at sensory test mean ± SD	94.2 ± 39.7	81.9 ± 21.4	0.143 <sup>b</sup>
Stereoacuity, no. (%)			
60 arcsec or better	12/26 (46.2)	62/83 (74.7)	0.007 <sup>c</sup>
80 arcsec or worse	14/26 (53.8)	21/83 (25.3)	
Distance suppression, no. (%)	12/26 (46.2)	10/83 (12.0)	<0.001 <sup>c</sup>

E6 group, patients with infantile exotropia that occurred at ≤6 months of age; L6 group, patients with infantile exotropia that occurred at >6 months of age; SD, standard deviation.

<sup>a</sup>Log-rank test.

<sup>b</sup>Independent *t* test.

<sup>c</sup>χ<sup>2</sup> test.

constant deviation was 60.0% in the E6 group, which was greater than that in the L6 group (40% [*P* = 0.045]) (Table 2). Mean time from the first visit to surgery was 8.2 months in the E6 group and 4.8 months in the L6 group (*P* = 0.193). Monthly progression rate of exodeviation from the first visit to surgery was comparable between groups (−1.8<sup>Δ</sup> in the E6 groups vs 0.0<sup>Δ</sup> in the L6 group [*P* = 0.108]).

### Motor and Sensory Outcomes

During a mean follow-up of 4.6 years, recurrence was observed in 12 (34%) patients in the E6 group and 38 (38%) in the L6 group; overcorrection, in 3 (9%) patients in the E6 group and 4 (4%) in the L6 group. These differences were not statistically significant between groups (Table 3).

Of the included 134 patients, 109 (81.3%) were eligible for analysis of sensory outcomes. Mean age at sensory test was 94.2 months in the E6 group and 81.9 months in the L6 group, which was not significantly different (*P* = 0.143). However, the proportion of reduced stereoacuity was greater in the E6 group compared with the L6 group (54% vs 25% [*P* = 0.007]). Furthermore, suppression was more pronounced in the E6 group than in the L6 group (46% vs 12% [*P* < 0.001]). See Table 3.

The rate of amblyopia was comparable between groups at the final examination, noted in 8 patients (23%) in the E6 group and 18 (18%) in the L6 group (*P* = 0.548).

### Analysis of Reduced Stereopsis and Suppression

Logistic regression analysis demonstrated higher odds of onset ≤6 months for reduced stereoacuity (OR = 6.42; 95% CI, 1.67-24.70) and suppression (OR = 37.67; 95% CI, 2.69-526.56). However, there was no significant associ-

ation of exotropia onset with recurrence or overcorrection (Table 4).

As the results showed significant correlation of constant deviation with reduced stereoacuity and distant suppression, we conducted further subgroup analysis, considering patients with constant exotropia (n = 45) and those with intermittent exotropia (n = 64) among 109 patients eligible for sensory analysis. In both exotropia subgroups, the proportions of reduced stereoacuity and distant suppression were greater in infantile exotropia patients with onset of ≤6 months than in patients with onset of >6 months. Statistical significance was found in the categories of distance suppression in the constant exotropia subgroup and reduced stereoacuity in the intermittent exotropia subgroup (Table 5). Logistic regression analysis confirmed the correlations between earlier onset and distance suppression in the constant exotropia group (OR = 215.69; 95% CI, 1.77-26282.85) and between earlier onset and reduced stereoacuity in the intermittent exotropia group (OR = 14.88; 95% CI, 1.66-133.26). See Table 6.

## Discussion

We evaluated surgical outcomes in infantile exotropia according to age of deviation onset. Our results suggest that earlier age of onset (≤6 months) is an independent factor that affects near stereoacuity and distance fusional status, and that it is not associated with motor outcomes.

Although an exodeviation can be observed in the first few weeks of life, eyes begin to straighten until 2-4 months of age as the vergence system matures. Exodeviations that persist beyond 6 months of age are considered abnormal.<sup>5,11-15</sup> Primary infantile exotropia, defined by onset before 6 months, reflects deficient development of the convergence system and disruption of normal binocular processing in the visual cortex.<sup>11,13,16</sup> Therefore, it could be reasonably postulated that the surgical prognosis of infantile exotropia depends on whether exotropia onset is before or after 6 months of age. Nevertheless, to our knowledge, no previous study has compared surgical outcomes of patients with infantile exotropia grouped by age of onset.

Although high levels of binocular function could be achieved in patients with infantile exotropia, previous research has reported decreased binocular sensory function in early-onset exotropia compared to that of childhood intermittent exotropia.<sup>3,5,6,9,17,18</sup> In the present study, bifoveal fixation with stereoacuity of at least 60 arcsec was achieved in 67.9% of patients (74/109) for whom sensory outcomes was possible. In the E6 group, this proportion was only 46%, which was significantly lower than 75% in the L6 group. Moreover, the proportion of patients with suppression was higher in the E6 group than that in the L6 group. In logistic regression analysis, earlier onset age of ≤6 months was independently associated with suppression and reduced stereopsis, suggesting that exotropia

Table 4. Multivariate logistic regression analysis of motor and sensory outcomes after surgery for infantile exotropia

Patient characteristic	Adjusted OR (95% CI)			
	Motor outcome		Sensory outcome	
	Recurrence	Overcorrection	Reduced stereoacuity	Distance suppression
Onset age				
≤6 months	0.55 (0.20-1.49)	3.39 (0.56-20.53)	6.42 (1.67-24.70)	37.67 (2.69-526.56)
>6 months	1 [reference]	1 [reference]	1 [reference]	1 [reference]
Female sex	0.59 (0.27-1.30)	1.59 (0.27-9.33)	0.45 (0.14-1.48)	0.04 (0.00-0.63)
Duration of XT, per month	1.01 (0.99-1.03)	1.00 (0.96-1.04)	0.98 (0.95-1.02)	0.96 (0.90-1.03)
Pre-op angle of deviation, per PD	1.00 (0.90-1.11)	0.6 (0.78-1.19)	1.06 (0.89-1.25)	1.20 (0.80-1.81)
Constant deviation	1.99 (0.87-4.55)	0.40 (0.06-2.49)	4.21 (1.30-13.70)	31.31 (1.36-722.66)
DVD	5.01 (1.57-16.00)	0.47 (0.03-6.47)	— <sup>a</sup>	— <sup>b</sup>
Overelevation in adduction	0.48 (0.16-1.38)	1.19 (0.15-9.32)	— <sup>a</sup>	208.00 (1.50-28794.09)
Refractive errors, per D	1.31 (0.91-1.88)	1.07 (0.52-2.19)	0.81 (0.60-1.09)	1.34 (0.54-3.31)
Presence of anisometropia	1.76 (0.27-11.37)	— <sup>c</sup>	0.35 (0.02-5.89)	— <sup>b</sup>
Reduced recession	0.69 (0.29-1.63)	2.21 (0.31-15.84)	0.84 (0.22-3.17)	0.18 (0.01-3.48)
Presence of amblyopia	0.64 (0.22-1.87)	0.48 (0.04-5.44)	1.24 (0.24-6.43)	0.21 (0.01-4.48)
Age at sensory test, per month	—	—	0.99 (0.96-1.02)	1.01 (0.95-1.07)
Deviation at sensory test, per PD	—	—	1.05 (0.90-1.23)	1.36 (1.06-1.73)

CI, confidence interval; D, diopter; DVD, dissociated vertical deviation; OR, odds ratio; PD, prism diopter; XT, exotropia.

<sup>a</sup>ORs and 95% CIs could not be calculated: none of the patients in this category had DVD or overelevation in adduction.

<sup>b</sup>ORs and 95% CIs could not be calculated: none of the patients in this category had DVD or anisometropia.

<sup>c</sup>ORs and 95% CIs could not be calculated: none of the patients in this category had anisometropia.

Table 5. Reduced stereoacuity and distance suppression after infantile exotropia surgery according to the onset time in each subgroup

Postoperative result	Constant exotropia at examination			Intermittent exotropia at examination		
	E6 group (n = 13)	L6 group (n = 32)	P value	E6 group (n = 13)	L6 group (n = 51)	P value
Reduced stereoacuity, <sup>a</sup> no. (%)	8 (61.5)	15 (46.9)	0.372 <sup>b</sup>	6 (46.2)	6 (11.8)	0.011 <sup>c</sup>
Distance suppression, no. (%)	9 (69.2)	7 (21.9)	0.005 <sup>c</sup>	3 (23.1)	3 (5.9)	0.092 <sup>c</sup>

E6 group, infantile exotropia patients with onset age ≤6 months; L6 group, infantile exotropia patients with onset age >6 months.

<sup>a</sup>80 arcsec or worse.

<sup>b</sup> $\chi^2$  test.

<sup>c</sup>Fisher exact test.

Table 6. Adjusted odds of earlier onset age for risk of reduced stereoacuity and distance suppression in each subgroup according to constancy at examination

Risk	Adjusted OR <sup>a</sup> of earlier onset, age ≤6 months (95% CI)	
	Constant XT	Intermittent XT
Reduced stereoacuity <sup>b</sup>	1.15 (0.16-8.17)	14.88 (1.66-133.26)
Distance suppression	215.69 (1.77-26282.85)	2.03 <sup>c</sup>

CI, confidence interval; OR, odds ratio; XT, exotropia.

<sup>a</sup>Covariates in logistic regression analyses included sex, duration of exotropia, preoperative deviation, dissociated vertical deviation, overelevation in adduction, refractive errors, anisometropia, type of surgery, amblyopia, age at sensory test, and deviation angle at sensory test.

<sup>b</sup>80 arcsec or worse.

<sup>c</sup>95% CI was not calculated in this category.

onset before 6 months of age may affect central fusion and binocularity.

The results of subgroup analysis also demonstrated worse sensory outcomes in infantile exotropia patients

with age of onset of ≤6 months in both of the constant and intermittent exotropia subgroups. Nevertheless, only distance suppression in the constant exotropia subgroup and reduced stereoacuity in the intermittent exotropia subgroup were statistically significant. This could be attributable to the small number of patients in each subgroup, which may also explain the wide confidence intervals of odds ratios in logistic regression analysis. Studies with larger samples are needed to verify the significance of our findings.

Our analysis used results of stereoacuity testing performed after age 5. Although Birch and colleagues<sup>19</sup> have suggested that stereoacuity of 60 arcsec or better could be achieved by age 7 years, the proportions of patients in our cohort with stereoacuity of at least 60 arcsec were comparable between patients aged 5-7 years and those >7 (45/70 vs 29/39 [ $P = 0.280$  by  $\chi^2$  test]). Furthermore, we included age at sensory test in our logistic regression model, and the mean age at sensory testing was comparable between the two groups. Nevertheless, given the results of previous studies on longitudinal changes in stereoacuity,<sup>19-21</sup> it might be necessary to observe the change of

stereoacuity with age in patients with infantile exotropia through longer follow-up.

Results of the Titmus stereo test and Vectogram could be influenced by ocular conditions at the time of examination, including refractive errors, presence of amblyopia, and horizontal/vertical ocular deviations.<sup>22-25</sup> Moreover, presence of constant deviation and duration of strabismus also could affect the surgical outcomes of exotropia.<sup>26,27</sup> Therefore, to determine the independent correlation between exotropia onset  $\leq 6$  months of age and sensory outcomes, we included those factors into multivariate logistic regression analysis.

In previous studies on infantile exotropia, age of onset was not found to be associated with surgical outcomes.<sup>7,28</sup> However, the majority of patients in those studies did not reach a sufficient age to cooperate with testing for stereoacuity or sensory fusion; therefore, only motor outcomes, such as recurrence or overcorrection, could be evaluated, and the onset of exotropia seemed not to be associated with surgical outcomes in these studies.

In our cohort, recession was reduced in 37% of the E6 group and in 51% of the L6 group ( $P = 0.173$ ) by 1.0–2.0 mm over the conventional dosage to lower the risk of overcorrection. Because this was a retrospective study, procedures were not randomized to patients; nevertheless, the surgical motor outcomes were similar according to surgical methods. During the study period, the recurrence rate was 39% in the conventional surgery group and 35% in the reduced recession group ( $P = 0.793$ ), and the overcorrection rate was 4% in the conventional surgery group 6% in the reduced recession group ( $P = 0.593$ ). This result was consistent with that of our previous study, in which reduced recession did not affect final motor outcomes.<sup>29</sup> The sensory outcomes were also similar between the conventional and reduced-recession group ( $P = 0.350$  for reduced stereoacuity and  $P = 0.594$  for distant suppression [data not shown]). More importantly, we included type of surgery as a covariate in multivariate analyses when drawing the adjusted odds ratio of early onset  $\leq 6$  months for surgical motor and sensory outcomes.

The recurrence rate was higher than the overcorrection rate in this study. It could be that the higher recurrence rate is attributable to insufficient surgical amounts. In a previous report on the effect of augmented bilateral lateral rectus recession for childhood intermittent exotropia,<sup>30</sup> the recurrence rate was 49% in the original surgery group and 37% in the augmented surgery group at a mean follow-up of 4.0 years. Although it is difficult to compare the results of the current study with those of the previous one, in which the characteristics of the enrolled subjects, post-operative management, and surgeons differed, the recurrence rates were similar. Further research comparing the surgical outcomes of augmented, conventional, and reduced recession will help to determine appropriate surgical amounts for infantile exotropia.

This study has several limitations. First, the precise age of onset could not be determined, although an effort was

made to review as many photographs as possible to determine at least whether age of onset was before or after 6 months. Second, as mean age at onset of exotropia in the E6 group was 2.4 months, it could be argued that exotropia reported to be observed before 3–4 months of age might not be distinguished from transient infantile deviation.<sup>11-14</sup> For this reason, we focused on whether the onset was before or after 6 months and the onset age was treated as a categorical variable in the analysis rather than a real value. Third, we could not assess whether the patients initially showed intermittent or constant deviation. Therefore, we used constancy at examination for the analyses in this study. A longitudinal observational study from birth is necessary to evaluate the control level of infantile exotropia patients at initial presentation and its effect on the prognosis of infantile exotropia. Other limitations include the study's retrospective design and the relatively small number of subjects.

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