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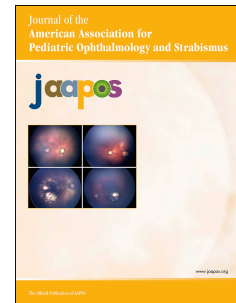
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Change in the eye position under general anesthesia in children with intermittent exotropia

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Abstract

Purpose

To evaluate the eye position in subjects with intermittent exotropia and normal subjects under general anesthesia (GA) using the strabismus photo analyzer.

Methods

This retrospective case–control study included 78 subjects with intermittent exotropia and 25 normal control subjects who underwent epiblepharon surgery. Eye position under GA was assessed using the strabismus photo analyzer, based on eye models generated from corneal lights and limbus in pre- and post-anesthesia images. Eye positions under GA in the control and intermittent exotropia groups were compared. Preoperative angle of deviation was also compared with amount of change in eye position under GA in the intermittent exotropia group.

Results

Eye position under GA was more divergent in subjects with intermittent exotropia than in controls ($P = 0.008$). The amount of change in eye position under GA was correlated with the preoperative angle of deviation ($r^2 = 0.47$; $P < 0.001$). In small preoperative exodeviations, the change in eye position was primarily more divergent, whereas in large exodeviations, a convergent tendency—less exotropic compared with the preoperative angle of exodeviation—was observed.

Conclusions

In subjects with small preoperative exodeviations, there was a tendency for eye position to become more divergent after GA; in those with large exodeviations, there was less exotropia after GA.

The etiology of intermittent exotropia remains unclear, but a combination of anatomical and innervational factors is likely.¹⁻⁴ Evaluating the position of the eyes under general anesthesia (GA) can be useful as a measurement of the resting eye position without innervational vergence tonus.⁵⁻⁷ In general, eye position after GA is divergent in normal subjects and subjects with exotropia.⁸⁻¹¹ However, several have reported inconsistent results regarding the relationship between the preoperative angle of deviation and eye position under GA in subjects with exotropia⁸⁻¹³; the inconsistency could be due to the lack of objectivity in the examiner-dependent measurements of eye position, such as Hirschberg or Krimsky tests. Using the photographic method, several trials have attempted to interpret the Hirschberg test in a quantitative and objective manner as the Hirschberg ratio, defined as the ratio of the angle of ocular deviation to the displacement of corneal reflex. However, the Hirschberg ratio has large variability, from 7° to 16° (12^Δ-28^Δ/mm).¹⁴⁻¹⁶

In 2012 Yang and colleagues¹⁶ developed the three-dimensional (3D) strabismus photo analyzer (Seoul National University R&DB Foundation, Seoul, Republic of Korea). This computerized software automatically quantifies the angle of strabismus from photographs, showed excellent agreement with the Krimsky test, and substantially improved reproducibility. In addition, it presents the angle of deviation directly in degrees and prism diopters, based on a 3D eye model that does not require conversion through a constant Hirschberg ratio.¹⁶ The purpose of this study was to use the strabismus photo analyzer to evaluate eye position under GA of subjects with intermittent exotropia compared with normal control subjects.

Subjects and Methods

The study was approved by the Seoul National University Hospital Institutional Review Board. In this retrospective case–control study, post-anesthesia preoperative patients with intermittent

exotropia who underwent strabismus surgery and control patients who underwent epiblepharon surgery at Seoul National University Children's Hospital between March 2016 and August 2016 were analyzed. Exclusion criteria were as follows: major ocular disease other than intermittent exotropia or epiblepharon, systemic disorders (eg, neurologic disorders), cycloplegic refractive errors of $> \pm 6$ D, constant exotropia, horizontal deviation $> 50^\Delta$,¹⁶ vertical deviation in the primary position, A or V pattern strabismus, and previous ocular surgeries.

Angles of deviation were measured using the alternate prism and cover test, with fixation targets at 1/3 m and 6 m, before surgery by two ophthalmologists (SJK and EHJ), and the orthophoric alignments were confirmed in the control group by two ophthalmologists (SJK and EHJ). The following information was collected through a review of medical records: sex, age at surgery, cycloplegic refraction, type of exotropia, presence of eye dominance, and lateral incomitance, and ocular torsion in fundus photography.¹⁷ Lateral incomitance was defined as a decrease of $> 5^\Delta$ in the distance deviation in lateral gaze.

Pre- and Post-anesthesia Photographs

For pre-anesthesia images, each subject's head was stabilized in the sitting position, and the subject was asked to look at a fixation target at 1/3 m. Infrared images were captured using the supernight shot mode of a video camera (HDR-HC7; Sony Electronics Inc, Tokyo, Japan) at a distance of 1 m from the subject.^{16,18} The supernight shot mode was selected to activate the infrared light illumination mounted originally in the camera in order to reduce the noise from the visible light. For subjects with intermittent exotropia, two images were captured—when fusion occurred and when fusion was broken. The former were obtained to help measurement of post-anesthesia deviation (Figure 1). Here, fusion was considered present when the eyes were grossly aligned by external observation. Infrared images breaking the fusion using an occluder with the

HOYA R72 filter (Kenko Tokina Co Ltd, Tokyo, Japan) in front of either eye were obtained to evaluate the pre-anesthesia angle of deviation using the strabismus photo analyzer.¹⁸ The HOYA R72 filter blocks all light with wavelengths <720 nm; thus, the occluder completely blocked the subject's view.¹⁸

Inhalational GA was administered for all surgeries. The GA was induced with 5 mg/kg intravenous thiopental sodium after administration of atropine (0.02 mg/kg). After ensuring adequate mask ventilation, rocuronium (0.6 mg/kg) was administered.¹⁹ Manual ventilation was performed with 4–8 vol% sevoflurane in 100% oxygen using a facemask. After full muscle relaxation, an endotracheal tube was inserted. Anesthesia was maintained with 6–8 vol% desflurane.

A post-anesthesia image after endotracheal intubation was obtained 2 min after the rocuronium injection. A full-face infrared image was captured with the patient in a supine position using the supernight shot mode of a video camera (FDR-AXP55; Sony Electronics Inc) with the HOYA 55 mm R72 infrared filter (Kenko Tokina Co Ltd, Tokyo, Japan) at a distance of 1 m from the subject.

Assessment of Eye Position under GA by Strabismus Photo Analyzer

The pre- and post-anesthesia two-dimensional (2D) images were preprocessed, registered, and analyzed semiautomatically using the strabismus photo analyzer; the mechanisms and procedures for which have been detailed elsewhere.^{16,18}

The eye position under GA was measured by the 3D strabismus photo analyzer as follows: the corneal light reflex (first Purkinje image) and limbus were detected from the pre-anesthesia photograph when fusion occurred (Figure 1A). The corneal diameter was estimated from the 2D images of each eye. Two separate spheres—the spheres of the eye and cornea—were simulated,

and a 3D eye model was generated using the age-adjusted normative proportion of the transverse corneal diameter, anterior chamber, and axial length.¹⁶ The angle k of each eye was calculated from the primary image. After post-anesthesia image registration (Figure 1B), the operator rotated the eyeball of the 3D model manually until its visual axis matched that of the processed image (Figure 1C-D). The software measured the deviated angle of each eye individually.¹⁶ The added angle of deviation for each eye was defined as the angle of deviation under GA.

Data Analysis

All measurements using the strabismus photo analyzer were performed twice by two observers (EHJ and YHK). The intra- and interobserver agreements were evaluated by calculating the intraclass correlation coefficient (ICC). The agreement between the angle of deviations measured by alternate prism and cover test and the strabismus photo analyzer was calculated as the ICC.

We compared eye position under GA of subjects with intermittent exotropia and normal controls. Additionally, the intermittent exotropia patients were classified into divergent and convergent groups, according to change of angle of deviation after GA compared with preoperative angle of deviation. The divergent group was defined as patients having a more divergent change after GA compared with preoperative angle of exodeviation; the convergent group, as patients having a decrease in angle of exodeviation after GA as compared with preoperative angle. The amount of change in eye position in GA was defined as the difference between the angle of deviation before and after GA. A positive value indicates a more exotropic position than preoperative angle of exodeviation after GA; a negative value indicates a less exotropic position. The clinical characteristics and eye position under anesthesia were compared between groups using an independent t test and the χ^2 test. Pearson correlation and linear regression analyses were performed to assess the correlation between the preoperative angle of

deviation and the post-anesthesia angle of deviation or amount of change in eye position. All statistical analyses were performed using the Statistical Package for Social Sciences, version 23.0 for Windows (SPSS Inc, Chicago, IL). P values of <0.05 were considered significant. The Bonferroni method was used to correct P values in case of multiple comparisons.

Results

Table 1 provides the characteristics in both study groups. The mean age of subjects was 7.0 ± 2.4 years (range, 2-14) in the intermittent exotropia group and 6.2 ± 2.0 years (range, 4-10) in the control group. There was no significant difference in age at surgery, male-to-female ratio, or refractive errors between groups.

The average preoperative angle of deviation was $26.9^\Delta \pm 6.3^\Delta$ (range, 12^Δ - 42.5^Δ) at distance and $29.5^\Delta \pm 6.8^\Delta$ (range, 15^Δ - 50^Δ) at near fixation in the intermittent exotropia group. All control subjects showed a divergent eye position under GA, with a mean eye of $21.8^\Delta \pm 6.6^\Delta$. The mean eye position under GA was more divergent in the intermittent exotropia group ($26.6^\Delta \pm 8.2^\Delta$) than in the control group ($P = 0.008$).

The mean changes in eye position under GA were $21.8^\Delta \pm 6.6^\Delta$ (range, 9.6^Δ - 34.6^Δ) in the control group and $-0.3^\Delta \pm 11.1^\Delta$ (range, -24.5^Δ to 32.1^Δ) in the intermittent exotropia group ($P < 0.001$).

There was excellent agreement in inter- and intraobserver variability and reliability of different methods (eSupplement 1, available at jaapos.org).

Preoperative Angle of Deviation versus Angle of Deviation under GA in Intermittent Exotropia

The eye position under GA showed a variable deviation (range, 7.7^Δ - 47.1^Δ) in the intermittent exotropia group. There was no correlation between the preoperative angle of deviation at distance fixation and the angle under GA ($r = -0.16$; $P = 0.17$; see Figure 2). However, there was

a significant correlation between the preoperative angles of deviation at distance fixation (X) and the amount of change in eye position under GA (Y) in the intermittent exotropia group ($r = 0.69$; $P < 0.001$; see Figure 3), with a tendency for eye position to change direction with respect to the preoperative angle. In small preoperative exodeviations, the eye position was primarily more divergent, whereas in large exodeviations a convergent tendency—less exotropic compared with the preoperative angle of exodeviation—was observed. This relationship can be approximated by the linear regression formula $Y = -1.20 \cdot X + 32.09$ ($r^2 = 0.47$; $P < 0.001$; see Figure 3).

Comparison of Subjects with Divergent and Convergent Changes in Eye Position

There was no significant difference in the age at surgery, sex, mean refractive error, lateral incomitance, fixation preference, change of laterality in the mainly deviated eye under GA, type of exotropia, and ocular torsion between the divergent- and convergent-change groups. Although 43% of those exhibiting a divergent-change had lateral incomitance compared with only 20% in the convergent-change group, this did not reach statistical significance. Fundus photographs were available for 70 of the 78 patients with intermittent exotropia, and 21 had ocular torsion.

The mean preoperative angle of deviation at distance and near fixation in the convergent-change group was significantly larger than that in the divergent-change group ($29.8^\Delta \pm 5.4^\Delta$ vs $23.9^\Delta \pm 5.8^\Delta$ and $32.6^\Delta \pm 6.3^\Delta$ vs $26.1^\Delta \pm 5.6^\Delta$, resp.; both $P < 0.001$). In addition, the mean angle of deviation under GA was $21.1^\Delta \pm 5.3^\Delta$ in the convergent-change group, which was significantly smaller than that in the divergent-change group ($32.5^\Delta \pm 6.3^\Delta$; $P < 0.001$) but similar to that in control subjects ($21.8^\Delta \pm 6.6^\Delta$; $P = 0.643$).

Discussion

In this study, we evaluated the eye position under GA in subjects with intermittent exotropia and in normal control subjects and the relation between the preoperative angle of deviation and

change in the eye position under GA.

Because the axes of orbits are oriented laterally, the anatomical positions of the eyes at resting status in subjects with orthophoria and exotropia are divergent in general.^{8-12,20} Because the normal resting position of the eyes is the exodeviated position, extraocular muscle tonus in the form of phoria adaptation plays a vital physiologic role in establishing binocular alignment.^{21,22} Brodsky²² and Brodsky and Jung²³ asserted that tonic control of the baseline divergent anatomical position may require phoria adaptation as a source for the tonic convergence that gives rise to tenacious proximal fusion.

In previous studies, eye position after administration of GA varied in subjects with exotropia; the position was generally more divergent under anesthesia compared with the preoperative angle. Moreover, eye position before and after anesthesia showed a positive linear correlation in some studies.^{8,9,11} However, some studies showed more convergent change under GA. Ohmi and colleagues¹³ reported that of 80 subjects with exotropia, 57 showed divergence, 6 showed no change, and 17 showed a change from exo- to esodeviation by Krimsky method combined with photography. Ku and colleagues¹² reported that subjects with exotropia of $<30^\Delta$ showed primarily divergence under GA, whereas subjects in exotropia of $>30^\Delta$ showed convergence by the photographic method. Similarly, small preoperative exodeviations showed a primarily more divergent tendency, whereas large exodeviations showed a convergent tendency in our study. Additionally, our study demonstrated a correlation between the preoperative angles of deviation and the amount of change in eye position under GA.

Duane⁴ proposed that exodeviations are caused by an innervational imbalance that upsets the reciprocal relationship between active convergence and divergence mechanisms. However, Bielschowsky introduced the concept of the abnormal position of rest associated with

exodeviations, which is determined by anatomical factors.³ A majority of the current theories on the etiology of exodeviation involve a combination of mechanical and innervational factors.¹ Although Burian² believed that intermittent exotropia was caused by an active divergent mechanism, Jampolsky⁵ argued that divergence is passive and a relaxation of convergence.²¹ And Brodsky and Jung²³ noted that it may reflect the existence of a central convergence center alone. The presence or absence of active divergence is still controversial.²⁴ In our study, eye position under GA was significantly more divergent in patients with intermittent exotropia than in control subjects, suggesting the involvement of mechanical factors of intermittent exotropia. Divergent change under GA could be explained by an imbalance in the mechanical and innervational factors that maintain ocular alignment by convergence. Considering the convergent change observed in our study, the large angle of deviation in cases of intermittent exotropia could be caused, at least in part, by an active divergence mechanism.

It is likely that the eye position under anesthesia is close to the anatomical resting position. The clinically functional resting position when awake is achieved by the tonic vergence system; however, it is not yet clear whether other systems are also involved. Although there are individual differences in the anatomical resting position, it is unlikely that exotropia is simply the result of convergence tonus in patients whose angle of exodeviation is greater than the anatomical resting position. Other than patients whose large longstanding exotropia is associated with lateral rectus contracture, patients with large exotropia are likely to have a more divergent functional resting position than anatomical resting position. This could be due to an active divergence mechanism or to an abnormality in the phoria adaptation system, which determines the resting position when awake.

In the present study, the strabismus photo analyzer showed excellent agreement with the

alternate prism and cover test and substantially improved reproducibility, which was comparable to previous studies.^{16,18} This finding supports the accuracy of the angle of deviation under GA reported in our study.

This study has several limitations. First, although previous study demonstrated that the 3D strabismus photo analyzer is a reliable tool for measuring the angle of strabismus, the use of the strabismus photo analyzer is limited, because anthropological ophthalmic biometry is applied and angle k is assumed to be symmetric. For simplicity, we included patients without vertical deviation, and only the horizontal angular distance, not the vertical deviation, was analyzed.¹⁶ Second, we only included patients who had undergone strabismus surgery; small-exotropia patients not requiring surgeries might not necessarily show similar findings under GA. Third, we could not prove that full muscle relaxation occurred at a standardized time after rocuronium injection. Although rocuronium, a nondepolarizing neuromuscular relaxant, provides excellent intubating conditions within 30-60 seconds in young children, the onset of action on the extraocular muscle is unknown.²⁵ To counter this limitation, we obtained post-anesthetic photographs at the same time (2 minutes) after rocuronium injection. Fourth, we did not use forced duction testing to assess lateral rectus muscle tightness under GA. Finally, photographs before and after GA were not taken in the same position, although a small-to-moderate amount of cyclotorsion was observed after the transition from the seated to the supine position.²⁶ Despite these limitations, our findings will help in understanding the pathogenesis of intermittent exotropia.

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Legends

FIG 1. Measurement of eye position following general anesthesia (GA) using pre- and post-anesthesia photographs. A, The pre-anesthesia infrared image was obtained when the subject's fusion occurred. The corneal light reflex and limbus were detected, and two separate spheres, the spheres of the eye (white dot line) and cornea (black dot line), were simulated. B, The post-anesthesia image was registered on analyzer. The black dot lines were the previous eye position of the pre-anesthesia images when fusion occurred. The yellow dot lines were the limbus of the post-anesthesia images. The operator rotated the eyeball of the 3D model manually until the pre-anesthesia sphere of the cornea (black dot lines) matched that of the registered post-anesthesia image (yellow dashed lines). C, The pre-anesthesia sphere of the cornea in the right eye (black dotted line) moved up to the post-anesthesia sphere of the cornea (yellow dashed line; black arrowhead in B). D, The same procedure was repeated on the left eye (B, black arrow). The software measured the angle of deviation of each eye, respectively.¹⁶ Added angle of deviation of each right and left eye was defined as the angle of deviation under general anesthesia.

FIG 2. Scatterplots showing the preoperative angle of deviation and angle of deviation under GA in the intermittent exotropia group. The eye position under GA showed variable deviation (range, 7.7^{Δ} - 47.1^{Δ}). There was no significant correlation between the preoperative angle of deviation at distant fixation and the angle of deviation under GA in subjects with intermittent exotropia ($r = -0.16$; $P = 0.171$).

FIG 3. Relationship between the preoperative angle of deviation and change of eye position under GA. A significant correlation was observed between the preoperative angles of deviation (X) and the amount of change in eye position under GA (Y) in the patients with IXT ($r = -0.69$; $r^2 = 0.47$; $P < 0.001$).

Table 1. Comparison of characteristics: control and intermittent exotropia groups

Study parameter	Control group ^a (n = 25)	Intermittent exotropia group ^a (n = 78)	P value
Age at surgery, years	6.2 ± 2.0 (4 to 10)	7.0 ± 2.4 (2 to 14)	0.093 ^b
Sex (M : F)	10 : 15	36 : 42	0.590 ^c
Mean refractive error, D	-0.5 ± 1.5 (-4.1 to 2.0)	-0.5 ± 1.6 (-5.9 to 4.4)	0.894 ^b
Preoperative deviation			
Distance	0	26.9 ± 6.3 (12 to 42.5)	<0.001 ^b
Near	0	29.5 ± 6.8 (15 to 50)	<0.001 ^b
Preoperative deviation by 3D strabismus analyzer, PD	0.6 ± 1.0 (0.0 to 4.0)	29.0 ± 6.7 (16.7 to 49.8)	<0.001 ^b
Angle of deviation under GA, PD	21.8 ± 6.6 (9.6 to 34.6)	26.6 ± 8.2 (7.7 to 47.1)	0.008 ^d
Amount of change of eye position under GA, PD	21.8 ± 6.6 (9.6 to 34.6)	-0.3 ± 11.1 (-24.5 to 32.1)	<0.001 ^d

D, diopter; GA, general anesthesia; PD, prism diopter.

^aExcept as noted, data presented as mean with standard deviation with range in parentheses.

^bMann-Whitney test.

^cPearson χ^2 test.

^dIndependent *t* test.

Table 2. Comparison of the characteristics of subjects whose changes in eye position under GA were divergent and convergent in the intermittent exotropia group

Study parameter	Divergent change (n = 38)	Convergent change (n = 40)	P value
Age at surgery, years	7.1 ± 2.6 (3 to 14)	6.8 ± 2.2 (2 to 12)	0.573 ^b
Sex (M : F)	18 : 20	18:22	0.834 ^c
Mean refractive error, D	-0.4 ± 1.6 (-4.8 to 4.4)	-0.6 ± 1.6 (-5.9 to 1.6)	0.600 ^b
Lateral incomitance, no.	17	8	0.019 ^c
Fixation preference, no.	19	24	0.375 ^c
Change of laterality of mainly deviated eye under GA, no.	2	4	0.678 ^d
Type of exotropia (basic : divergence excess)	35 : 3	37 : 3	1.000 ^d
Presence of ocular torsion, %	27	33	0.531 ^c
Preoperative deviation, PD			
Distance	23.9 ± 5.8 (12 to 40)	29.8 ± 5.4 (20 to 42.5)	<0.001 ^b
Near	26.1 ± 5.6 (15 to 40)	32.6 ± 6.3 (20 to 50)	<0.001 ^b
Angle of deviation under GA, PD	32.5 ± 6.3 (19.2 to 47.1)	21.1 ± 5.3 (7.7 to 29.9)	<0.001 ^b
Amount of change of eye position under GA, PD	8.6 ± 7.2 (0.4 to 32.1)	-8.7 ± 6.5 (-24.5 to -0.3)	<0.001 ^b

D, diopter; GA, general anesthesia; PD, prism diopter.

^aExcept as noted, data presented as mean with standard deviation with range in parentheses.

^bIndependent *t* test.

^cPearson χ^2 test.

^dFisher exact test.

