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Characteristic differences between full-term and premature infants with intermittent exotropia

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Strabismus is prevalent among preterm infants of low gestational age and birth weight in Southeast Asian countries, with intermittent exotropia (IXT) being the most common type in South Korea. In this retrospective, cross-sectional study, we investigated the differences between full-term and premature infants with IXT. IXT patients with available childbirth history were divided into two groups: preterm vs. full-term and low birth weight (LBW) vs. normal birth weight (NBW). Parameters related to exotropia including parental heredity, surgical history, and treatment options were investigated. In univariate regression for gestational age, a result of ≥ 100 s in the Titmus test was 1.352 times more frequent in preterm than in full-term infants. When birth weight was considered instead, a result of ≥ 100 s in the Titmus test was 1.412 times more frequent in the LBW compared to the NBW group. In multivariate regression for birth weight, the frequency of a result of ≥ 100 s in the Titmus test for the LBW group was 2.032 times higher than that for the NBW group. It is particularly important to examine stereopsis in preterm and LBW patients affected by IXT to ensure timely surgical planning and avoid potential recurrence after surgery.

Keywords Strabismus, Exotropia, Low gestational age, Low birth weight, Preterm infants

Visual defects, cerebral visual impairment, refractive errors, strabismus, color vision, and visual field defects are more commonly encountered in preterm infants than in full-term infants owing to the unfavorable effects of prematurity on neurological and visual development[1]. The prevalence of strabismus among preterm infants of low gestational age (LGA) and low birth weight (LBW) has been reported to be up to 42%[2–9]. The main risk factors for strabismus associated with LGA and LBW have been repeatedly discussed in the literature[8,10–16]. This topic has become increasingly significant with the increase in the survival rate of extremely preterm infants in recent years, necessitating further exploration[17,18].

Intermittent exotropia (IXT) is the most common type of strabismus in South Korea (prevalence of 1.1% ± 0.1% according to the Korea National Health and Nutrition Examination Survey data)[19] and several other Asian countries[20–23]. Therefore, this study aimed to investigate the differences between full-term and preterm infants with IXT by analyzing the age at admission, sex, onset of strabismus, diagnosis period, dominant eye, degree of control, stereopsis, presence of refractive error, parental heredity, surgery, and degree of refraction.

Methods

This was a retrospective, observational, cross-sectional, multicenter study. Participants were recruited from March 1, 2019, to February 29, 2020, by 65 strabismus specialists in 53 institutions, among which secondary or tertiary referral centers accounted for 98.1%. The study protocol conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Keimyung University Hospital (approval number: 2020-06-083). The Korean Intermittent Exotropia Multicenter Study (KIEMS), initiated by the Korean Association of Pediatric Ophthalmology and Strabismus (KAPOS), is a nationwide cross-sectional study investigating IXT in Korea. Questionnaires and examination forms were pre-distributed to the investigators to

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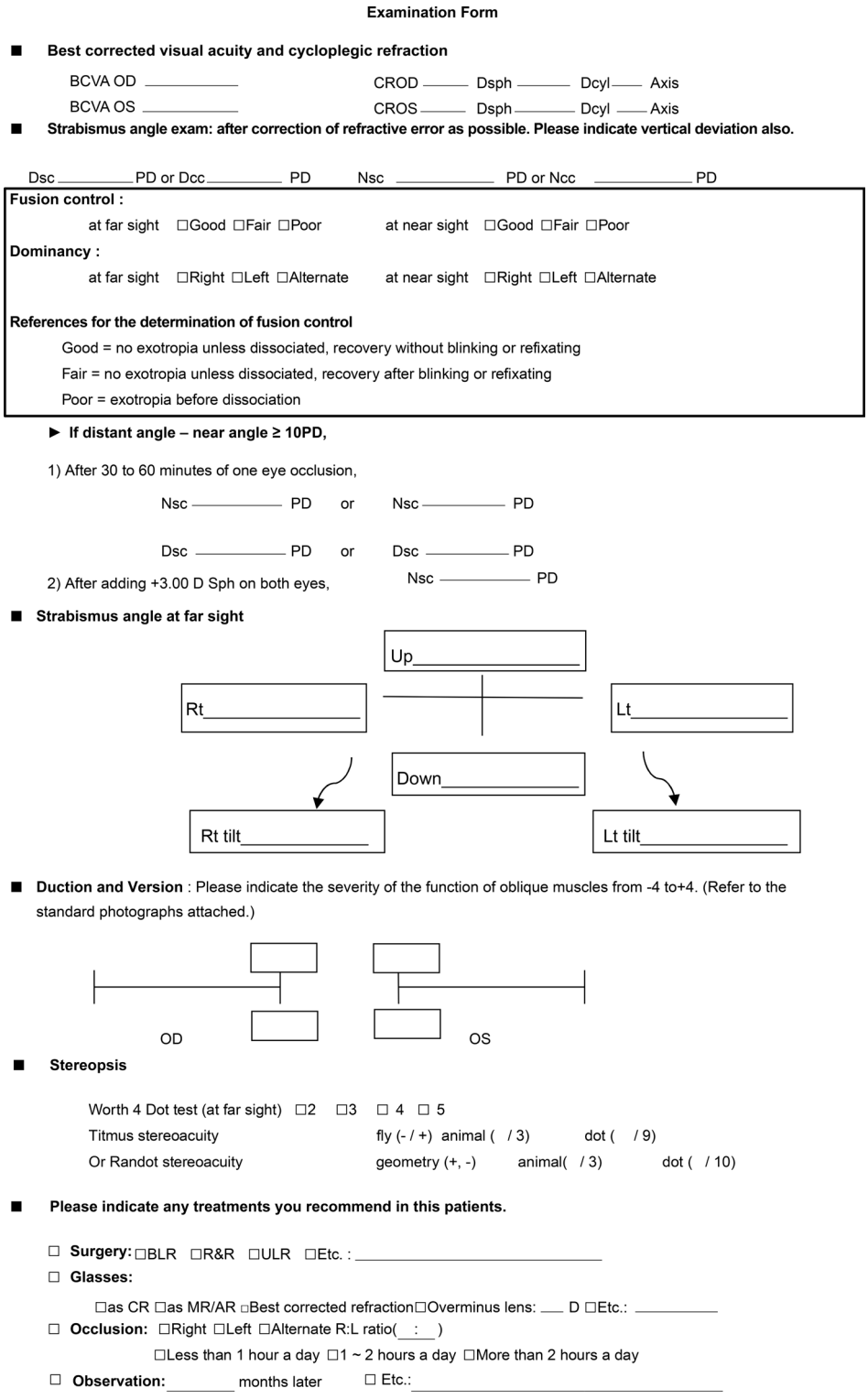
standardize data collection. Each investigator collected questionnaires and examination forms (Figs. 1, 2) from each patient with IXT[24]. The questionnaires and examination forms were collected by the KIEMS committee and handled centrally[24]. The IRB of Keimyung University Dongsan Hospital waived the requirement to obtain written informed consent due to the retrospective nature of the study. All institutions participating in the study were exempted from the requirement to obtain written informed consent through their respective IRB, and all received approval.

Questionnaire Form

Questions	Please check the appropriate box.
Who is writing this questionnaire?	☐Patient (self) ☐Mother ☐Father ☐Grandparent ☐Etc._____
What is the reason for this visit?	Answer:
Have you ever visited other clinics?	☐ No ☐ Yes Name of the clinic: _____ Previous diagnosis:_____
Have you ever noticed the ocular misalignment?	☐ Yes ☐ No ☐ Not sure
- Who found the symptom first? (Example: parents, teacher, doctor etc.)	Answer:
- When did you notice the symptom, first?	Answer: years ago (years of age)
How often do you notice the symptom in a day?	☐None ☐Less than once ☐More than once
What is the direction of the ocular misalignment?	☐Inward ☐Outward ☐Upward ☐Not sure ☐Etc.: _____
Which eye do you think misaligned?	☐None ☐Right ☐Left ☐Alternate ☐Not sure ☐Etc.:_____
Have you ever noticed abnormal head posture?	☐None ☐Tilt ☐Head turn ☐Etc. _____
How often do you notice the abnormal head posture?	☐ Always ☐ Sometimes ☐ Etc. _____
Please select all the symptoms which the patient present.	☐Frowning ☐Discomfort at near sight ☐Headache ☐Ocular pain ☐Visual blurring ☐None ☐Not sure ☐Things look smaller than they really are
Any diplopia at near sight?	☐None ☐Not sure ☐Less than once in a day ☐More than once in a day
Any diplopia at far sight?	☐None ☐Not sure ☐Less than once in a day ☐More than once in a day
Has the patient ever got occlusion therapy?	☐ Yes ☐ No
- Prescribed period and duration?	Period:_____ ~ _____ Duration in a day:_____
- Which eye?	☐ Right ☐ Left ☐ Alternate
- Real period and duration?	Period: _____ ~ _____ Duration in a day:_____
Does the patient wear the glasses?	☐ Never ☐ Yes Since when:_____
Has the patient ever got any type of surgery (including ocular surgery)?	☐ None ☐ Yes Name of the surgery:_____
Has the patient ever been diagnosed any medical condition? (Systemic disease, Developmental delay, ADHD, brain disease etc.)	☐ None ☐ Yes Diagnosis: _____
Questions about birth history.	☐ Normal spontaneous vaginal delivery ☐ Caesarean section ☐ Not sure
- Gestational age (weeks), birth weight (kg), prematurity?	Answer: ___ weeks ___ kg ☐ prematurity
- Any problems at birth? (example: breathing difficulty, lung disease, delivery complications)	☐ None ☐ Yes Diagnosis:_____
Does the patient's mother have any strabismus?	☐ No ☐ Yes (Diagnosis:_____) ☐ Not sure
- Any strabismus surgery history?	☐ No ☐ Yes ☐ Not sure
Does the patient's father have any strabismus?	☐ No ☐ Yes (Diagnosis:_____) ☐ Not sure
- Any strabismus surgery history?	☐ No ☐ Yes ☐ Not sure
Do the patient's siblings have any strabismus?	☐ No ☐ Yes (Diagnosis:_____) ☐ Not sure
- Any strabismus surgery history?	☐ No ☐ Yes ☐ Not sure

Fig. 1. Questionnaire form for patients with intermittent exotropia.


Examination Form

■ Best corrected visual acuity and cycloplegic refraction

BCVA OD _____ CROD ____ Dsph _____ Dcyl ____ Axis

BCVA OS _____ CROS ____ Dsph _____ Dcyl ____ Axis

■ Strabismus angle exam: after correction of refractive error as possible. Please indicate vertical deviation also.

Dsc _____ PD or Dcc _____ PD Nsc _____ PD or Ncc _____ PD

Fusion control :

at far sight ☐Good ☐Fair ☐Poor at near sight ☐Good ☐Fair ☐Poor

Dominancy :

at far sight ☐Right ☐Left ☐Alternate at near sight ☐Right ☐Left ☐Alternate

References for the determination of fusion control

Good = no exotropia unless dissociated, recovery without blinking or refixating

Fair = no exotropia unless dissociated, recovery after blinking or refixating

Poor = exotropia before dissociation

► If distant angle – near angle ≥ 10PD,

1) After 30 to 60 minutes of one eye occlusion,

Nsc _____ PD or Nsc _____ PD

Dsc _____ PD or Dsc _____ PD

2) After adding +3.00 D Sph on both eyes, Nsc _____ PD

■ Strabismus angle at far sight

Up_____

Rt_____ Lt_____

Down_____

Rt tilt_____ Lt tilt_____

■ Duction and Version : Please indicate the severity of the function of oblique muscles from -4 to+4. (Refer to the standard photographs attached.)

OD OS

■ Stereopsis

Worth 4 Dot test (at far sight) ☐2 ☐3 ☐ 4 ☐ 5

Titmus stereoacuity fly (- / +) animal (/ 3) dot (/ 9)

Or Randot stereoacuity geometry (+, -) animal(/ 3) dot (/ 10)

■ Please indicate any treatments you recommend in this patients.

☐ Surgery: ☐BLR ☐R&R ☐ULR ☐Etc. : _____

☐ Glasses:

☐as CR ☐as MR/AR ☐Best corrected refraction☐Overminus lens: ___ D ☐Etc.: _____

☐ Occlusion: ☐Right ☐Left ☐Alternate R:L ratio(__:__)

☐Less than 1 hour a day ☐1 ~ 2 hours a day ☐More than 2 hours a day

☐ Observation: _____ months later ☐ Etc.: _____

Fig. 2. Examination form for patients with intermittent exotropia.

Study population

The KIEMS multicenter study included 5385 patients with IXT[24]. The present study included patients with childbirth history (type of delivery, gestational age, and birth weight) described either by their parents or themselves.

A total of 4,066 patients were divided into two groups according to their gestational age. Infants with a gestational age of ≥ 37 weeks were classified as full-term, whereas those with a gestational age of < 37 weeks were classified as preterm.

A total of 4599 patients were divided into two groups according to birth weight. Infants weighing less than 2.5 kg were classified as LBW, while those with a birth weight of ≥ 2.5 kg were considered to have a normal birth weight (NBW).

Variables

The age at exotropia onset, sex, presence of refractive error, near and distance combined with vertical strabismus, near and distance exodeviation angle, degree of near and distance control, near and distance dominant eye, stereopsis (Worth 4 dots, Titmus, and Randot), parental heredity, surgical history, and treatment options were analyzed for each patient. The outcomes of the Titmus and Randot tests were divided according to their median value into two subgroups per test. The refraction data of the right and left eyes were converted into spherical equivalents (SE) and categorized into the myopia, emmetropia, and hyperopia groups. SE were calculated as Sphere + Cylinder/2. SE ≤ −0.5 D, − 0.5 D < SE < 1.0 D, and SE ≥ 1.0 D were defined as myopia, emmetropia, and hyperopia, respectively.

Statistical analyses

Data were analyzed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as percentages (%) to the extent of occupancy. Continuous variables (age, onset of exotropia, far prism diopter, and near prism diopter) are expressed as mean ± standard deviation. The significance level (α level) was determined using a two-tailed test at 0.05. Pearson's chi-square test or Fisher's exact test (only for paternal operation history) was used to ascertain whether an association existed between the preterm and full-term groups based on birth week. An independent *t*-test was used to identify significant differences in continuous variables between the groups.

Patients were divided into two groups according to their GA (Gestational Age) and BW (Birth Weight). Logistic regression analysis was performed subsequently to identify variables with significant associations. Birth weight or week, age at the onset of strabismus, parental strabismus, and parental strabismus surgery were adjusted for in the analysis.

Results

Among the enrolled patients, the average number of weeks for those with a GA over 37 weeks was 39.11 ± 1.43 weeks (range: 37 – 53 weeks), whereas for those with a GA under 37 weeks it was 32.99 ± 4.79 weeks (range: 20.0 – 36.4 weeks). The average weight for those with a BW over 2.5 kg was 3.24 ± 0.40 kg (range: 2.5 – 6.2 kg), whereas for those with a BW under 2.5 kg it was 2.00 ± 0.42 kg (range: 0.66 – 2.49 kg). There was a slight predominance of female patients in the study population (52% female versus 47% male). The refractive error results showed that myopia was less prevalent in the preterm and in the LBW groups compared to the full-term and NBW groups, whereas hyperopia was more prevalent instead. The results were only statistically significant in the case of the left eye, although the same pattern was revealed in all patient categories. Patient demographics are shown in Table 1.

Gestational age

Patients were divided into two groups according to the gestational age: ≥ 37 weeks (G1) and < 37 weeks (G2). Among the 4066 patients included in this study, 3493 belonged to the G1 group, whereas 573 belonged to the G2 group. The proportion of male infants in the G1 and G2 groups was 47.1 and 46.2%, respectively. The proportion of mothers with strabismus in the G1 and G2 groups was 5.0 and 4.1%, respectively. The proportion of mothers with a history of surgery in the G1 and G2 groups was 4.9 and 3.6%, respectively. The proportion of fathers with strabismus in the G1 and G2 groups was 4.9 and 3.5%, respectively. The proportion of fathers with a surgical history in the G1 and G2 groups was 2.9 and 2.0%, respectively; however, none of these differences were statistically significant. The ratios of far/near hypertropia were 10.9%/6.9% and 10.5%/5.4% in the G1 and G2 groups, with no significant differences observed between the two groups. No significant differences were observed between the two groups in the far/near control, far/near dominant eye, and the Worth 4 dot test. In the Titmus test, the proportion of infants with ≤ 80 s in the G1 and G2 groups was 55.4 and 47.8%, respectively, indicating statistical significance ($p = 0.007$). No significant difference was observed between the two groups in the Randot test. Similarly, no significant difference was observed between the ratio of surgical to nonsurgical treatments in the two groups. Regarding refraction, there was no significant difference in the right eye; however, the percentage of myopia in the left eye was 42.5 and 40.4% in the G1 and G2 groups, respectively, and the percentage of myopia in G1 was significantly higher ($p = 0.037$). The distance/near deviation angles in the G1 group were 23.04 ± 8.39/24.46 ± 8.85 PD, respectively, and that in G2 group were 23.18 ± 7.90/23.82 ± 8.98 PD. The difference between the two groups was not statistically significant (Table 1).

No statistically significant differences were observed in either the univariate and the multivariate regression analyses, except for those corresponding to the refractive error, Titmus test results, and far dominant eye. After adjusting for birth weight in the univariate analysis, the risk of hyperopia was 1.4420 times higher in the preterm group compared to the full-term group ($p = 0.016$), but only in the left eye. The probability of attaining a Titmus result of ≥ 100 s was 1.3524 times higher in the preterm compared to the full-term group ($p = 0.007$). After adjusting for birth weight, the age of strabismus onset, parental strabismus, and parental strabismus surgery in the multivariate analysis, the number of cases in which the far dominant eye alternated was 0.69 times lower in the preterm compared to the full-term group ($p = 0.046$; Table 2).

		Gestational age					Birth weight				
		Full-term (n = 3493)		Premature (n = 573)			Full-term (n = 4227)		Premature (n = 388)		
		N (%) (mean)	(SD)	N (%) (mean)	(SD)	*p*-value	N (%) (mean)	(SD)	N (%) (mean)	(SD)	*p*-value
Age, years (mean ± SD)		6.661	4.129	7.101	5.094	0.022*	7.028	4.598	6.865	5.195	0.509
Onset of exotropia (mean ± SD)		4.699	3.526	4.929	4.890	0.200	4.925	3.720	4.861	5.262	0.769
Sex	Male	1646	47.12	265	46.25	0.697	2021	47.81	162	41.75	0.022*
	Female	1847	52.88	308	53.75		2206	52.19	226	58.25	
Hx of strabismus in mother	Yes	170	4.97	23	4.09	0.365	199	4.81	18	4.70	0.920
Hx of strabismus in father	Yes	168	4.94	20	3.57	0.157	188	4.58	16	4.20	0.732
Surgical Hx of mother	Yes	68	4.62	7	2.78	0.185	76	4.08	6	3.70	0.818
Surgical Hx of father	Yes	43	2.89	5	2.04	0.455	52	2.76	2	1.25	0.435
Refraction (Rt.)	Myopia	1063	42.03	166	39.34	0.245	1323	43.04	111	39.78	0.094
	Emmetropia	1027	40.61	169	40.05		1226	39.88	106	37.99	
	Hyperopia	439	17.36	87	20.62		525	17.08	62	22.22	
Refraction (Lt.)	Myopia	954	42.51	155	40.36	0.037*	1195	43.89	105	39.62	0.029*
	Emmetropia	940	41.89	149	38.80		1102	40.47	102	38.49	
	Hyperopia	350	15.60	80	20.83		426	15.64	58	21.89	
Far hypertropia	Yes	379	10.85	60	10.47	0.786	476	11.26	42	10.82	0.794
Near hypertropia	Yes	242	6.93	31	5.41	0.178	300	7.10	27	6.96	0.919
Far prism diopter		8.388	23.04	7.903	23.18	0.708	8	23.13	8.492	23.33	0.660
Near prism diopter		8.848	24.46	8.979	23.82	0.109	9	24.64	9.321	23.67	0.043
Far control	Good	852	27.22	131	25.84	0.800	1038	27.45	81	23.48	0.238
	Fair	1312	41.92	215	42.41		1560	41.25	155	44.93	
	Poor	966	30.86	161	31.76		1184	31.31	109	31.59	
Near control	Good	1319	43.94	201	41.44	0.582	1561	43.15	132	39.52	0.380
	Fair	1088	36.24	185	38.14		1326	36.65	134	40.12	
	Poor	595	19.82	99	20.41		731	20.20	68	20.36	
Far dominant	Alternative	1455	48.13	236	47.77	0.883	1761	48.15	161	48.49	0.906
	One eye	1568	51.87	258	52.23		1896	51.85	171	51.51	
Near dominant	Alternative	1752	60.98	284	61.74	0.757	2105	60.93	197	61.76	0.771
	One eye	1121	39.02	176	38.26		1350	39.07	122	38.24	
W4D	Normal	1222	49.78	189	47.97	0.506	1520	50.45	119	47.04	0.297
	Abnormal	1233	50.22	205	52.03		1493	49.55	134	52.96	
Titmus (s)	≤ 80	1293	55.37	178	47.85	0.007**	1605	55.44	111	46.84	0.010*
	≥ 100	1042	44.63	194	52.15		1290	44.56	126	53.16	
Randot	≤ 50	367	57.25	48	52.17	0.358	448	58.26	28	46.67	0.080
	≥ 63	274	42.75	44	47.83		321	41.74	32	53.33	
Operation plan	Yes	1734	49.64	300	52.36	0.228	2163	51.17	180	46.39	0.072
Glasses plan	Yes	953	27.28	172	30.02	0.175	1172	27.73	126	32.47	0.047*
Patch plan	Yes	1070	30.63	164	28.62	0.332	1225	28.98	117	30.15	0.626
Observation plan	Yes	829	23.73	125	21.82	0.315	983	23.26	85	21.91	0.547

Table 1. Patient distribution and demographics. *Hx* history, *W4D* worth 4 dot, *SD* standard deviation. *$p < 0.05$; ** $p < 0.01$.

Birth weight

The patients were divided into two groups according to the birth weight: ≥ 2.5 kg (G1) and < 2.5 kg (G2), with a total cohort of 4615 (4227 were G1 and 388 G2). Regarding sex, the proportion of males in the G1 and G2 groups was 47.8 and 41.8%, respectively, indicating statistical significance (p = 0.022).

The proportion of mothers with strabismus was 4.8 and 4.7% in the G1 and G2 groups, respectively. The proportion of fathers with strabismus was 4.1 and 3.7% in the G1 and G2 groups, respectively; however, the difference was not statistically significant. The proportion of mothers who underwent strabismus surgery was 4.6 and 4.2% in the G1 and G2 groups, respectively; however, this minor difference was not statistically significant. The percentage of fathers who underwent strabismus surgery was 2.8 and 1.3% in the G1 and G2 groups, respectively; however, no significant differences were observed between the groups. The ratios of far/near hypertropia were 11.3%/7.1% and 10.8%/7.0% in the G1 and G2 groups, respectively, with no significant differences observed between the two groups. No significant differences were observed between the two groups in the far/near control, far/near dominant eyes, or Worth 4 dot test. The proportion of infants with < 80 s in the Titmus test was 55.4 and 46.8% in the G1 and G2 groups, respectively, indicating a statistically significant difference ($p = 0.010$). No significant differences were observed between the two groups in the Randot test, ratio of surgery, occlusion, and

Characteristics		Univariate			Multivariate		
		OR	95% CI	*p*-value	OR	CI	*p*-value
Weight (kg)		0.0718	(0.057, 0.090)	< 0.0001**			
Onset age (years)		1.0153	(0.992, 1.039)	0.2016			
Mother Strabismus	No	Ref					
	Yes	0.8145	(0.522, 1.271)	0.3661			
Mother Operation hx	No	Ref					
	Yes	0.5895	(0.268, 1.299)	0.1897			
Father Strabismus	No	Ref					
	Yes	0.7123	(0.444, 1.143)	0.1593			
Father Operation hx	No	Ref					
	Yes	0.7011	(0.275, 1.788)	0.4571			
Refraction (Rt.)	Myopia	Ref					
	Emmetropia	0.9490	(0.754, 1.195)	0.6564	1.5044	(0.976, 2.318)	0.0642
	Hyperopia	1.2043	(0.909, 1.596)	0.1959	1.4360	(0.828, 2.491)	0.1978
Refraction (Lt.)	Myopia	Ref					
	Emmetropia	1.0250	(0.805, 1.306)	0.8416	1.4747	(0.923, 2.355)	0.1040
	Hyperopia	1.4420	(1.070, 1.943)	0.0161*	1.3006	(0.713, 2.373)	0.3915
Far hypertropia	No	Ref					
	Yes	0.9610	(0.721, 1.282)	0.7864	0.7982	(0.458, 1.390)	0.4260
Near hypertropia	No	Ref					
	Yes	0.7684	(0.523, 1.129)	0.1795	0.5872	(0.272, 1.269)	0.1756
Far prism diopter		1.0020	(0.992, 1.013)	0.7083	1.0027	(0.983, 1.023)	0.7912
Near prism diopter		0.9918	(0.982, 1.002)	0.1091	0.9991	(0.981, 1.017)	0.9231
Far control	Good	0.9383	(0.743, 1.185)	0.5931	1.2387	(0.798, 1.924)	0.3407
	Fair	Ref					
	Poor	1.0171	(0.816, 1.268)	0.8805	1.1978	(0.796, 1.803)	0.3868
Near control	Good	0.8962	(0.723, 1.111)	0.3183	1.1015	(0.733, 1.655)	0.6415
	Fair	Ref					
	Poor	0.9785	(0.752, 1.274)	0.8719	1.1652	(0.725, 1.873)	0.5278
Far dominant	One eye	Ref					
	Alternative	0.9858	(0.815, 1.193)	0.8827	0.6941	(0.485, 0.993)	0.0455*
Near dominant	One eye	Ref					
	Alternative	1.0325	(0.843, 1.264)	0.7570	0.7420	(0.510, 1.080)	0.1190
W4D	Normal	Ref					
	Abnormal	1.0750	(0.869, 1.330)	0.5056	0.8136	(0.544, 1.216)	0.3147
Titmus	≤ 80	Ref					
	≥ 100	1.3524	(1.086, 1.684)	0.0069**	1.0588	(0.703, 1.594)	0.7842
Randot	≤ 50	Ref					
	≥ 63	1.2278	(0.792, 1.903)	0.3584	1.0941	(0.471, 2.544)	0.8346
Operation plan	No	Ref					
	Yes	1.1147	(0.934, 1.330)	0.2286	0.8539	(0.615, 1.186)	0.3461
Glasses plan	No	Ref					
	Yes	1.1432	(0.942, 1.387)	0.1753	1.1961	(0.833, 1.716)	0.3313
Patch plan	No	Ref					
	Yes	0.9080	(0.747, 1.103)	0.3319	1.2866	(0.907, 1.825)	0.1573
Observation plan	No	Ref					
	Yes	0.8966	(0.725, 1.110)	0.3154	1.2308	(0.833, 1.819)	0.2974

Table 2. Logistic regression analysis by gestational age. Multivariate analysis: Adjusted birth week, onset age, presence/absence of strabismus in the parents, Parents' surgical history. *$p < 0.05$; **$p < 0.01$. *CI* confidence interval, *OR* odds ratio, *W4D* worth 4 dot, *hx* history.

follow-up between the surgical and nonsurgical treatments. The proportion of patients who required glasses was 27.7 and 32.5% in the G1 and G2 groups, respectively, indicating that the prescription rate of glasses was significantly higher in the G2 group ($p = 0.047$). Regarding refraction, no significant difference was observed in the right eye; however, the ratio of myopia in the left eye was significantly higher in G1 compared with that in

G2 (43.9 vs. 39.6%; $p = 0.029$). The distance/near deviation angles in the G1 group were 23.13 ± 8.43/24.64 ± 9.00 PD, respectively, and those in G2 were 23.33 ± 8.50/23.67 ± 9.32 PD. No significant difference was observed in the distance angle of deviation; however, the G1 deviation angle at the near angle was statistically significantly larger ($p = 0.043$; Table 1).

In the logistic regression analysis, a statistically significant difference was identified in the univariable test for refractive error, near prism diopter, Titmus test results, and wearing glasses. In the multivariate regression analysis, distant control, Titmus, and patch treatment differed significantly (Table 3).

After adjusting for gestational age in the univariate analysis, the risk of hyperopia was 1.4710 times higher in the LBW than in the NBW group ($p = 0.027$), especially in left eye refraction. Near prism diopter was 0.9880 times lower in the LBW compared to the NBW group ($p = 0.042$). Furthermore, Titmus result of ≥ 100 s in the LBW was 1.4123 times higher than that of the NBW ($p = 0.011$). And LBW glass plan is 1.2536 times more than NBW ($p = 0.047$).

After adjusting for gestational age, the age of strabismus onset, parental strabismus, and parental strabismus surgery in the multivariate analysis, the risk of "poor" far control in the LBW group was 0.4883 times lower than in the NBW group ($p = 0.008$). The frequency of a Titmus test result of ≥ 100 s in the LBW group was 2.032 times higher than that in the NBW group ($p = 0.010$). A patch plan was 0.557 times less frequent in the LBW group.

Discussion

Previous studies have reported that the prevalence of strabismus in LBW children (< 1500 g) is 12–36%, compared to 2–6% in the general population[13,14,25–32].

Another study conducted by the Avon Longitudinal Study of Parents and Children examined the effects of gestational age alone after adjusting for birth weight and found that prematurity (gestational age of < 37 weeks) increased the risk of esotropia by 2.5-fold but did not affect the risk of exotropia[13].

The KIEMS, initiated by the KAPOS, is a nationwide cross-sectional study investigating IXT in Korea[24]. Based on previous research, this study compared the variables of age at admission, sex, strabismus onset time, diagnosis period, dominant eye, degree of control, stereopsis, presence of refractive error, parental heredity, surgery, degree of refraction, and treatment options using gestational age and weight in patients with IXT.

The results of this study showed that the ratio of Titmus < 80 s in the full-term group was 1.352 times that of the preterm group. The Titmus test and the Randot test were used to measure stereoacuity at each hospital participating in this multicenter study. In general, the Titmus test was preferred, leading to a higher number of Titmus test results. Therefore, although in both cases the outcome suggested that stereoacuity was lower in premature infants, statistical significance was only achieved in the case of the Titmus test. Unification of the test used to evaluate stereoacuity is recommended for the future. Myopia was also higher in the full-term group in the left eye refraction test than that in the preterm group. Furthermore, multivariate regression analysis revealed that the number of cases in which the far dominant eye alternated was 0.69 times lower in the pre-term group compared to the full-term group. Due to the fact that this was a retrospective study, we only determined whether the IXT patients exhibited alternate fixation or not, but not which eye was the dominant one. Therefore, the analysis of the laterality was incomplete in future studies, additional information regarding stereoacuity will be obtained by determining the dominant eye, and its relationship with refraction and visual acuity.

The above findings reveal that preterm infants, based on gestational age or birth weight, tend to use one eye more than normal infants, and have poor stereoscopic vision. Some studies have shown that preterm infants requiring treatment for retinopathy of prematurity (ROP) and/or neurological problems at 2.5 years are more likely to have slightly poorer stereoacuity. Preterm infants without these problems also had reduced stereoacuity compared with controls, possibly caused by undetected cerebral lesions in the early neonatal period, as cerebral problems are associated with poor stereoacuity[33,34]. Since this was a retrospective study and the questionnaire used to collect the data did not include a question about ROP, it was not possible to determine which of the participants had a history of ROP. However, if the ROP treatment can be assessed in future prospective studies, its potential relationship with stereoscopic vision problems may be evaluated. Determining whether these problems are caused by a developmental impairment in the brain is a potentially interesting avenue for future research. Previous papers have reported lower stereoacuity in individuals with strabismus, amblyopia, or anisometropia[35,36]. Hellgren et al.[37] reported that preterm infants with very LBW had significantly worse stereoacuity than controls at adolescence. This is comparable to a study by Lindqvist et al.[28], where 74% of LBW adolescents had normal stereoacuity compared with 83% of the controls. The findings of our study align with those of the study by Petursdottir et al.[38], as preterm-born young adults were more likely to manifest strabismus than full-term-born controls. These individuals also had impaired stereoacuity, even after excluding individuals with heterotropia and neurological problems at 2.5 years[38]. These results suggested that stereopsis in preterm infants was worse compared to healthy infants, regardless of the presence of strabismus or neurological problems. This finding is consistent with the results of our thesis, where patients with IXT were corrected for strabismus. Thus, the presence or absence of a preterm birth must be evaluated when a patient with IXT visits a hospital. If the patient is a preterm baby, even after treatment, such as strabismus correction, stereopsis should be well managed to reduce the number of recurrences by using only one eye with additional occlusion treatment or supplementary treatments that can improve stereopsis. Since it could be hypothesized that the postoperative recurrence rate is high in premature infants due to lack of stereoacuity, future studies should focus on measuring this recurrence rate in patients with IXT. Additionally, in this multicenter study, the presence and timing of patches according to the angle of strabismus were determined at the first visit in patients with intermittent exotropia. As this was a retrospective study, the patch was determined separately from amblyopia, and therefore it did not reflect it. It would be be interesting to evaluate patch plans in relation to amblyopia in future prospective studies.

Characteristics		Univariate			Multivariate		
		OR	95% CI	*p*-value	OR	CI	p-value
Birth week		0.668	(0.642, 0.695)	< 0.0001 **			
Onset age (years)		0.996	(0.967, 1.025)	0.7688			
Mother Strabismus	No	Ref					
	Yes	0.975	(0.595, 1.598)	0.9205			
Mother Surgical hx	No	Ref					
	Yes	0.905	(0.388, 2.112)	0.8181			
Father Strabismus	No	Ref					
	Yes	0.913	(0.542, 1.538)	0.7319			
Father Surgical hx	No	Ref					
	Yes	0.447	(0.108, 1.851)	0.2665			
Refraction (Rt.)	Myopia	Ref					
	Emmetropia	0.970	(0.735, 1.281)	0.8318	0.925	(0.530, 1.613)	0.7838
	Hyperopia	1.366	(0.982, 1.899)	0.0637	0.998	(0.497, 2.003)	0.9954
Refraction (Lt.)	Myopia	Ref					
	Emmetropia	0.949	(0.714, 1.262)	0.7200	0.921	(0.514, 1.654)	0.7840
	Hyperopia	1.471	(1.046, 2.069)	0.0266*	1.106	(0.539, 2.267)	0.7834
Far hypertropia	No	Ref					
	Yes	0.957	(0.685, 1.336)	0.7945	1.207	(0.620, 2.348)	0.5795
Near hypertropia	No	Ref					
	Yes	0.979	(0.651, 1.473)	0.9190	0.728	(0.272, 1.950)	0.5275
Far prism diopter		1.003	(0.991, 1.015)	0.6598	1.008	(0.983, 1.033)	0.5319
Near prism diopter		0.988	(0.977, 1.000)	0.0424*	0.997	(0.975, 1.020)	0.8063
Far control	good	0.785	(0.594, 1.039)	0.0908	0.706	(0.411, 1.214)	0.2084
	fair	Ref					
	poor	0.927	(0.717, 1.197)	0.5598	0.488	(0.288, 0.829)	0.0079**
Near control	good	0.837	(0.651, 1.076)	0.1645	0.718	(0.440, 1.171)	0.1843
	fair	Ref					
	poor	0.921	(0.678, 1.249)	0.5951	0.605	(0.334, 1.097)	0.0978
Far dominant	One eye	Ref					
	Alternative	1.014	(0.810, 1.269)	0.9056	0.682	(0.439, 1.061)	0.0900
Near dominant	One eye	Ref					
	Alternative	1.036	(0.818, 1.311)	0.7714	0.770	(0.486, 1.219)	0.2646
W4D	Normal	Ref					
	Abnormal	1.146	(0.887, 1.482)	0.2974	1.212	(0.724, 2.029)	0.4653
Titmus (s)	≤ 80	Ref					
	≥ 100	1.412	(1.083, 1.842)	0.0108*	2.032	(1.182, 3.494)	0.0103*
Randot	≤ 50	Ref					
	≥ 63	1.595	(0.942, 2.702)	0.0825	1.445	(0.553, 3.778)	0.4523
Operation plan	No	Ref					
	Yes	0.826	(0.670, 1.017)	0.0719	0.889	(0.591, 1.337)	0.5718
Glasses plan	No	Ref					
	Yes	1.254	(1.003, 1.567)	0.0469*	1.172	(0.751, 1.830)	0.4845
Patch plan	No	Ref					
	Yes	1.058	(0.843, 1.327)	0.6260	0.557	(0.344, 0.902)	0.0173*
Observation plan	No	Ref					
	Yes	0.926	(0.720, 1.190)	0.5469	0.968	(0.588, 1.592)	0.8977

Table 3. Logistic regression analysis by gestational age. Multivariate analysis: Adjusted birth week, onset age, presence/absence of strabismus in the parents, Parents' surgical history. *$p < 0.05$; **$p < 0.01$. *W4D* worth 4 dot, *hx* history, *CI* confidence interval, *OR*, odds ratio.

Our results also consistently showed that the incidence of hyperopia was higher in the left eye in preterm infants, with a statistically significant difference in the average age observed between the preterm and full-term groups using gestational age ($p = 0.022$). In terms of weight, no statistically significant difference in the average age was observed between the preterm and full-term groups using birth weight ($p = 0.509$). O'Connor et al.[1]

reported that ophthalmological defects are more common in preterm than full-term children, with lower visual acuity and increased risk of refractive errors, as well as ROP observed in the neonatal period. Although full-term infants demonstrated higher myopia rates in our study, including an increased risk of refractive errors, this was a retrospective study. The age at the initial visit was approximately 7 years old (range 0.3–70 years old), and the results may have been affected by the presence of other diseases not recorded in the study. Future studies must include patients with additional axial length and implement age restrictions.

Some additional results were obtained in addition to birth weight and gestational age. First, the proportion of women with LBW (< 2.5 kg) was high, indicating that women with IXT might be LBW. There was a trend towards a higher proportion of women among patients with intermittent exotropia, and although this was not statistically significant in terms of genetics, it suggests that strabismus and a history of strabismus surgery on the mother's side rather than on the father's side may have a slightly greater effect on intermittent exotropia. Prospective research on genetics is warranted in the future. If a genetic relationship is confirmed, it will contribute to explain the influence of strabismus and surgical history in the parents on the prevalence and prognosis of IXT. Collecting data on the incidence of IXT in the parents of children affected by IXT would also be important to shed light on this issue.

Although previous studies have reported that the prevalence of strabismus is higher in premature infants[25–32], the probability of developing strabismus and the size of the angle of strabismus may be separate, and the near angle of strabismus can be approximately 1D less in premature infants. The number of patients who required glasses in the preterm group was 1.254 times that of the full-term group. This is similar to the findings of a previous report that revealed more severe visual problems in preterm children than in children born at full term, with lower visual acuity and an increased risk of refractive errors being observed in the neonatal period[1]. Furthermore, the operation plan was 49% in the full-term group versus 52% in the preterm group (although the difference was not statistically significant). This could be a reflection of poorer stereoacuity in the preterm group, leading to an early decision for surgery. However, the operation plan in the LBW group was lower than that in the NBW group (46% versus 51%, p-value: 0.07). In our study, the decision to perform surgery was based on objective criteria (degree, angle, and age of stereoacuity) as well as in the subjective judgment of the practitioner at the time of the first visit. Some differences in stereoacuity were identified in premature infants in terms of age and angle at the time of visit, among others. Since subjective judgment partially relies on these differences, this introduces a potential source of bias. In the future, it will be more appropriate to conduct research by prospectively determining not only the time of the first visit but also the extent of future surgeries.

Fusion control of IXT of the eyes was 'normal' rather than 'poor' and stereoacuity was worse in premature infants; however, Rosenbaum and Santiago[39] reported that near stereoacuity did not differ significantly between patients with intermittent exotropia and normal controls. No correlation was observed with the degree of fusion control. As in the present study, although the babies were born preterm, the degree of strabismus was normal rather than poor. In addition, a higher risk of occlusion treatment was observed, consistent with our findings that premature babies have poor stereopsis and mainly use only one eye according to the number of weeks and weight.

Previous studies have mainly explained the high probability of strabismus in preterm babies. However, to the best of our knowledge, no large-scale studies on IXT have been conducted. Nevertheless, this study has some limitations. First, only patients with IXT were included in this study, which may limit the generalizability of the findings to other types of strabismus. Second, the study relied on cross-sectional data, which limits its ability to draw conclusions regarding causality or temporality. Lastly, this study relied on self-reported data, which may have introduced bias or measurement errors. Despite these limitations, this study is the first to compare premature infants with healthy infants diagnosed with IXT. IXT is prevalent in most Asian countries, including Korea[19–23]. The survival rate of premature babies is increasing with the recent developments in technology and medical care; therefore, this study is of great significance. Gestational age and birth weight must be determined in patients with IXT. It is particularly important to examine stereopsis in preterm and LBW patients affected by IXT to ensure timely surgical planning and avoid potential recurrence after surgery.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare no competing interests.

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