IXT Workshop Handout

IXT1 - A Randomized Trial Comparing Bilateral Lateral Rectus Recession versus Unilateral Recess and Resect for Basic-Type Intermittent Exotropia

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A Randomized Trial Comparing Bilateral Lateral Rectus Recession versus Unilateral Recess and Resect for Basic-Type Intermittent Exotropia

*Pediatric Eye Disease Investigator Group**
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Purpose: To compare long-term outcomes after bilateral lateral rectus recession (BLRc) or unilateral lateral rectus recession combined with medial rectus resection in the same eye (R&R) for primary treatment of childhood intermittent exotropia (IXT).

Design: Multicenter, randomized clinical trial.

Participants: One hundred ninety-seven children 3 to younger than 11 years of age with basic-type IXT, a largest deviation by prism and alternate cover test at any distance of 15 to 40 prism diopters (PD), and near stereoacuity of at least 400 seconds of arc.

Methods: Random assignment to BLRc or R&R and masked examinations conducted every 6 months after surgery for 3 years.

Main Outcome Measures: Proportion of participants meeting suboptimal surgical outcome by 3 years, defined as: (1) exotropia of 10 PD or more at distance or near using simultaneous prism and cover test (SPCT); or (2) constant esotropia of 6 PD or more at distance or near using SPCT; (3) loss of 2 octaves or more of stereoacuity from baseline, at any masked examination; or (4) reoperation without meeting any of these criteria.

Results: Cumulative probability of suboptimal surgical outcome by 3 years was 46% (43/101) in the BLRc group versus 37% (33/96) in the R&R group (treatment group difference of BLRc minus R&R, 9%; 95% confidence interval [CI], −6% to 23%). Reoperation by 3 years occurred in 9 participants (10%) in the BLRc group (8 of 9 met suboptimal surgical outcome criteria) and in 4 participants (5%) in the R&R group (3 of 4 met suboptimal surgical outcome criteria; treatment group difference of BLRc minus R&R, 5%; 95% CI, −2% to 13%). Among participants completing the 3-year visit, 29% (25 of 86) in the BLRc group and 17% (13 of 77) in the R&R group underwent reoperation or met suboptimal surgical outcome criteria at 3 years (treatment group difference of BLRc minus R&R, 12%; 95% CI, −1% to 25%).

Conclusions: We did not find a statistically significant difference in suboptimal surgical outcome by 3 years between children with IXT treated with BLRc compared with those treated with R&R. Based on these findings, we are unable to recommend one surgical approach over the other for childhood IXT. *Ophthalmology 2019;126:305-317 © 2018 by the American Academy of Ophthalmology*

Supplemental material available at www.aaojournal.org.

Intermittent exotropia (IXT) is the most common form of childhood-onset exotropia.[1] If untreated, IXT rarely can lead to loss of binocular vision and can have negative psychosocial consequences.[2,3] When there is poor fusional control of an exodeviation, surgery is often the treatment of choice.[4–6] The 2 most common surgical procedures are bilateral lateral rectus recession (BLRc) and unilateral lateral rectus recession combined with medial rectus resection in the same eye (R&R). However, there is no agreement as to which procedure provides the greatest likelihood of short-term and long-term success. We report herein the results of a large multicenter randomized trial comparing the effectiveness of BLRc with that of R&R for the surgical treatment of basic-type IXT in children who are 3 to younger than 11 years of age with 3 years of postoperative follow-up.

Methods

The study was supported through a cooperative agreement with the National Eye Institute, National Institutes of Health, Bethesda, Maryland, and was conducted according to the tenets of the Declaration of Helsinki by the Pediatric Eye Disease Investigator

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Group at academic- and community-based clinical sites. The protocol and Health Insurance Portability and Accountability Act−compliant informed consent forms were approved by institutional review boards, and a parent or guardian of each study participant gave written informed consent. An independent data and safety monitoring committee provided study oversight. The study is registered at www.clinicaltrials.gov (identifier, NCT01032603; accessed June 1, 2018). The full study protocol is available on the Pediatric Eye Disease Investigator Group web site (www.pedig.net; accessed June 1, 2018).

Eligibility

We enrolled children who were 3 to younger than 11 years of age with IXT who had not undergone previous strabismus surgery and had near stereoacuity of 400 seconds of arc or better on the Randot Preschool Stereotest (Stereo Optical Co, Chicago, IL). Eligibility and exclusion criteria are shown in Table 1, including 5 criteria specific to the magnitude of the IXT (manifest deviation; see item no. 2 in Table 1).

In addition to a primary cohort of basic-type IXT participants with angles ranging from 15 to 40 prism diopters (PD), the study had 2 secondary cohorts (participants with pseudodivergence excess-type IXT with 15- to 40-PD angles of deviation and participants with either basic or pseudodivergence excess-type IXT with larger angles of 45 to 50 PD that will be reported in a separate article). Pseudodivergence excess-type IXT was defined as a deviation at near that increased to within 10 PD of the distance deviation when measured either with +3.00-diopter (D) lenses (unless high accommodative convergence/accommodation (AC/A) ratio of 6:1 or more by −2.00-D gradient method in distance) or after 45 minutes of occlusion.

Enrollment and Randomization

At enrollment, near stereoacuity was measured using the Randot Preschool Stereotest at 1/3 m, control of the exodeviation was assessed at distance (6 m) and at near (1/3 m) using the Office Control Score,[7] which ranges from 0 (phoria) to 5 (constant exotropia; Table S2, available at www.aaojournal.org), and ocular alignment was assessed using the cover and uncover test, simultaneous prism and cover test (SPCT), and prism and alternate cover test (PACT) at distance (6 m) and at near (1/3 m). In addition, health-related quality of life (HRQOL) was assessed using the Intermittent Exotropia Questionnaire (IXTQ).[8] This questionnaire consists of 3 components that assess IXT-related HRQOL as reported by children (separate versions for those 5 to 7 years of age vs. those 8 years of age or older), the child's HRQOL as perceived by the parents (proxy), and the parents' own HRQOL on 3 subscales on psychosocial, functional, and surgical domains. All components use Likert-type response scales and Rasch-based scoring[9,10] transformed to a 0 (worst HRQOL)-to-100 (best HRQOL) scale. On the day of surgery or the day before, participants were assigned randomly (using a permuted block design stratified by site) with equal probability to BLRc or R&R, using the study web site.

Surgical Procedures

Surgical dose was based on the largest preoperative exodeviation by PACT measurements at remote distance (at least 50 feet), distance (6 m), or near (1/3 m; Table 3). Surgeons could adjust the surgical dose within 1.0 mm for each muscle at their discretion to account for participant variables, such as lateral incomitance and age. Adjustable techniques were not permitted, and hangback techniques were allowed only if episcleral bites also were taken at the intended scleral insertion site. For R&R procedures, choice of eye was at investigator discretion. Data on surgical complications were collected at the 1-week and 8-week follow-up visits.

Follow-up Visits

Postoperative visits occurred at 1 week ± 3 days and 8 weeks ± 2 weeks, followed by masked examination visits at 6 months ± 1 month, and then every 6 months ± 2 months through 3 years after randomization. At each follow-up visit, a study-certified examiner (pediatric ophthalmologist, pediatric optometrist, or certified orthoptist) masked to the participant's treatment group measured stereoacuity, exotropia control, and ocular alignment. If 1 or more protocol-specified criterion for suboptimal surgical outcome (Table 4) was met on the initial masked examination testing, testing specific to that criterion was repeated by the masked examiner after a 10-minute break, with suboptimal surgical outcome declared only when both the test and repeat test results met the criteria. At 6-month and 3-year visits, HRQOL was reassessed using the IXTQ.[8]

Treatment during Postoperative Follow-up

If a constant esotropia of 6 PD or more by SPCT at distance and near was present at the 8-week postoperative visit, prism treatment was prescribed, selecting the minimum prism strength needed to neutralize the angle. At each subsequent visit, investigators were to attempt to reduce or discontinue prism at both distance and near. Other than prism treatment at 8 weeks, any nonsurgical treatment of any recurrent or residual exodeviation, esodeviation, or diplopia was at investigator discretion throughout the study. Reoperation or treatment with botulinum toxin were permitted only between 6 months and 3 years and only after criteria for suboptimal surgical outcome were met (Table 4).

Statistical Methods

The sample size of 189 participants provided 90% power with a type I error rate of 5% to detect a difference if the treatment group failure rate was 50% in the BLRc group versus 25% in the R&R group, assuming 10% loss to follow-up. The primary outcome was suboptimal surgical outcome by 3 years (originally termed *failure* and herein referred to as *suboptimal surgical outcome*), defined as: (1) 10 PD or more exotropia by SPCT at distance or near, (2) constant esotropia of 6 PD or more at distance or near, or (3) loss of 2 octaves or more of stereoacuity compared with baseline at any masked follow-up examination between 6 months and 3 years (Table 4). We chose SPCT because we believed that from the standpoint of motor alignment, a manifest tropia of specific magnitude was more important than the total deviation after dissociation. We allowed a small angle esotropia because some patients with IXT are primary monofixators and may have a small angle tropia both before and after surgery without diplopia. In addition, participants also were classified as having a suboptimal surgical outcome if they underwent reoperation without first meeting any of these criteria. For the primary analysis, the cumulative proportion of participants meeting criteria for suboptimal surgical outcome by 3 years was obtained using the Kaplan-Meier method and was compared between treatment groups using the Z test. A treatment group difference and a corresponding 95% confidence interval (CI) also were calculated.

Each of the 3 individual components of the suboptimal surgical outcome criteria was specified post hoc as a secondary outcome. These cause-specific outcomes differ from the primary outcome in 2 ways. The primary outcome refers to the first occurrence of any suboptimal surgical outcome criterion (or reoperation) being met, whereas the cause-specific outcomes refer to the first occurrence of a particular suboptimal surgical outcome criterion being met.

Table 1. Study Eligibility and Exclusion Criteria

Eligibility Criteria

1. Age 3 to <11 yrs.
2. Intermittent exotropia (manifest deviation) meeting all of the following:
   - Intermittent exotropia at distance or constant exotropia at distance and either intermittent exotropia or exophoria at near.
   - Exodeviation at least 10 PD at distance and near by PACT.
   - Exodeviation at least 15 PD at distance or near by PACT.
   - Largest exodeviation at distance, near, or remote distance between 15 and 40 PD (inclusive) by PACT.
   - Basic type (distance and near exodeviation within 10 PD by PACT).
3. Stereoacuity of 400 seconds of arc or better at near by Randot Preschool Stereotest (better of 2 measures if initial test shows worse than 40 seconds of arc).
4. Visual acuity in the worse eye 0.3 logMAR or better (20/40 by ATS HOTV for participants <7 yrs or 70 letters E-ETDRS testing for participants ≥7 yrs).
5. No hyperopia of more than +3.50 D SE in either eye.
6. Participants must be wearing spectacles or contact lenses for at least 1 week if refractive error (based on cycloplegic refraction performed within 6 mos before enrollment) meets any of the following:
   - Myopia >−0.50 D SE in either eye.
   - Anisometropia >1.00 D SE.
   - Astigmatism >2.00 D in either eye if ≤5 yrs and >1.50 D if >5 yrs.

   Refractive correction for participants meeting the above refractive error criteria must meet the following guidelines:
   - Anisometropia spherical equivalent must be within 0.25 D of full correction.
   - Astigmatism cylinder must be within 0.25 D of full correction and axis must be within 5 degrees of full correction.
   - For hyperopia, the spherical component can be reduced at investigator discretion provided the reduction is symmetrical. Prescribing any refractive correction to yield lenses that are more myopic than −0.50 D SE is considered deliberate overminus and is not allowed at enrollment. However, prescribing no correction or prescribing less than the full cycloplegic hyperopic correction (i.e., prescribing reduced plus) is not considered the same as overminusing for this protocol and is allowed because most participants without intermittent exotropia and hyperopic SE refractions in this range typically would not be prescribed a refractive correction.
   - For myopia, the intent is to fully correct, but the spherical component can be undercorrected by investigator discretion provided the reduction is symmetrical and results in no more than −0.50 D SE residual (i.e., uncorrected) myopia. Prescribing a correction that yields more than 0.50 D more minus SE than the cycloplegic refraction SE is considered deliberate overminus and is not allowed at enrollment.
   - Participants who have undergone treatment with prism or deliberate overminus refractive correction (as defined above) must have discontinued prism, any deliberate overminus, or both for at least 1 wk before enrollment.

   Note that the refractive correction guidelines and the requirement to wear refractive correction for at least 1 wk apply not only to participants who require refractive correction under the above criteria, but also to any other participant who is wearing refractive correction.
7. No atropine use within the last week.
8. Gestational age >34 wks.
9. Birth weight >1500 g.
10. Investigator plans to perform surgery, is willing to perform either surgical procedure and is not planning to use adjustable sutures.
11. Parent understands protocol, has agreed to surgery, and is willing to accept randomization to 1-eye surgery or 2-eye surgery.
12. Parent has home phone (or access to phone) and is willing to be contacted by coordinating center staff.
13. Relocation outside of area of an active PEDIG site within next 3 yrs is not anticipated.

Exclusion Criteria

1. Coexisting vertical deviation, oblique muscle dysfunction, DVD, or A or V pattern, any of which the investigator plans to address with vertical transposition of horizontal rectus muscles, oblique surgery, or vertical rectus muscle surgery; that is, only small vertical deviations, oblique muscle dysfunction, DVD, and A or V patterns not requiring surgery are allowed.
2. Limitation of ocular rotations resulting from restrictive or paretic strabismus.
3. Craniofacial malformations affecting the orbits.
4. Interocular visual acuity difference of more than 0.2 logMAR (2 lines on ATS HOTV for participants 3−<7 yrs or 10 letters on E-ETDRS for participants ≥7 yrs), investigator plans to initiate amblyopia treatment at this time, or both.
5. High AC/A ratio (exclude >6:1 by gradient method).
6. Prior strabismus surgery or botulinum toxin injection.
7. Ocular disorders that would reduce visual acuity (except refractive error).
8. Prior intraocular or refractive surgery.
9. Significant neurologic impairment such as cerebral palsy. Participants with mild speech or learning disabilities, or both are eligible.
10. Investigator planning to change refractive correction at this time (if the participant is otherwise eligible, the investigator should consider prescribing refractive correction and bringing the participant back at a later time for enrollment).

AC/A = accommodative convergence/accommodation; ATS = Amblyopia Treatment Study; D = diopter; DVD = dissociated vertical deviation; E-ETDRS = Electronic-Early Treatment of Diabetic Retinopathy Study; logMAR = logarithm of the minimum angle of resolution; PACT = prism and alternate cover test; PD = prism diopters; PEDIG = Pediatric Eye Disease Investigator Group; SE = spherical equivalent.

For each of the 3 cause-specific outcomes, participants who met any criteria other than the particular criterion being assessed remained at risk for the criterion of interest unless they underwent reoperation, in which case they were censored at the time of reoperation. The cumulative probability of each cause-specific outcome by 3 years and a 95% CI were obtained using the Kaplan-Meier method. It is acknowledged that the 3 cause-specific outcomes are not independent because reoperation is a competing risk for each (e.g., participants who met the exotropia outcome only and subsequently underwent reoperation were by definition

Table 3. Surgical Dose*

Magnitude of Largest Deviation by Prism and Alternate Cover Test (PD)	Amount to Recess Each Lateral Rectus Muscle (mm)†	Amount to Resect Medial Rectus Muscle (mm)†
Bilateral lateral rectus recession		
16	4.0	
18	5.0	
20	5.0	
25	6.0	
30	7.0	
35	7.5	
40	8.0	
Unilateral lateral rectus recession with medial rectus resection		
16	4.0	3.0
18	5.0	4.0
20	5.0	4.0
25	6.0	5.0
30	7.0	5.5
35	7.5	6.0
40	8.0	6.5

PD = prism diopters.
*Refers to largest angle by prism and alternate cover test at remote distance (at least 50 feet), distance (6 m), or near (1/3 m).
†For recessions, the measurement of surgical dose was to be made from the insertion of the muscle after muscle disinsertion. For resections, the measurement of surgical dose was to be made from the insertion of the muscle before muscle disinsertion.

censored without meeting the stereo loss or constant esotropia outcomes).

Additional secondary outcomes were suboptimal surgical outcome at the 3-year visit (prespecified) and complete or near-complete resolution (specified post hoc) at the 3-year visit. Suboptimal surgical outcome at the 3-year visit was defined as meeting any of the 3 suboptimal surgical outcome criteria at the 3-year visit (regardless of whether the criterion had been met at an earlier visit) or undergoing reoperation at any time. Complete or near-complete resolution was defined as meeting all of the following at the 3-year visit: (1) exodeviation of less than 10 PD (tropia or phoria) by both SPCT and PACT at distance and near and 10-PD or more reduction in PACT magnitude from the largest of the distance and near angles at enrollment, (2) esotropia of less than 6 PD at distance and near by SPCT, (3) no decrease in Randot Preschool Stereotest of 2 octaves or more from the enrollment stereoacuity or to nil, (4) no reoperation or treatment with botulinum toxin, and (5) no nonsurgical treatment for a recurrent or residual exodeviation. The proportion of participants with suboptimal surgical outcome at 3 years was compared between treatment groups using Barnard's exact test, and an exact 95% CI on the treatment group difference was calculated using Farrington-Manning scores.[11]

For all participants who completed the 3-year visit (regardless of whether they had undergone reoperation, whether they had a suboptimal surgical outcome by 3 years, or both), changes in exotropia control, PACT magnitude, and stereoacuity between baseline and the 3-year time points were compared between treatment groups in linear regression models that adjusted for the corresponding baseline value.

The cumulative proportion of reoperation by 3 years also was compared between treatment groups. Methods similar to the primary analysis were used.

For the each of the 2 age-specific versions of the child IXTQ, for the proxy questionnaire, and for each of the 3 parent questionnaire subscales, mean Rasch-based HRQOL scores[9,10] at 3 years were compared between treatment groups using the Wilcoxon rank-sum test.

All treatment group differences were calculated as the BLRc group minus the R&R group. Analyses were conducted using SAS software version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics

Between July 2010 and February 2014, 197 children were enrolled at 35 clinical sites, with 101 assigned to the BLRc group and 96 assigned to the R&R group (Fig 1). Mean age was 6.2±2.0 years,

Table 4. Definition of Suboptimal Surgical Outcome by 3 Years

Suboptimal surgical outcome by 3 yrs (primary outcome)
A participant's IXT was considered to be a suboptimal surgical outcome if at any visit occurring 6 mos or later, any of the following criteria are present by masked examiner testing:

1. Exotropia at distance or near at any time during the examination (i.e., can be constant or intermittent; determined by a cover-and-uncover test) with a magnitude of ≥10 PD by SPCT, confirmed by a retest.
2. Constant esotropia at distance or near (determined by at least 3 cover-and-uncover tests; one must be before any dissociation) with a magnitude of ≥6 PD by SPCT, confirmed by a retest.
3. Decrease in Randot Preschool Stereotest near stereoacuity ≥2 octaves (≥0.6 log arcsec) from enrollment, or to nil, confirmed by a retest (see table below).

Participants who underwent reoperation (or treatment with botulinum toxin) without first meeting any of the above suboptimal surgical outcome criteria also were counted as suboptimal surgical outcomes in the primary analysis.

Randot Preschool* Stereoacuity Thresholds for Suboptimal Surgical Outcome

Baseline Stereoacuity (arcsec)	*Stereoacuity Level Needed at Follow-up Visit to Meet Suboptimal Surgical Outcome Criteria (arcsec)*
40	200 or worse
60	400 or worse
100	400 or worse
200	800 or worse
400	Nil

arcsec = seconds of arc; IXT = intermittent exotropia; PD = prism diopter; SPCT = simultaneous prism and cover test.
*(Stereo Optical, Chicago, IL).

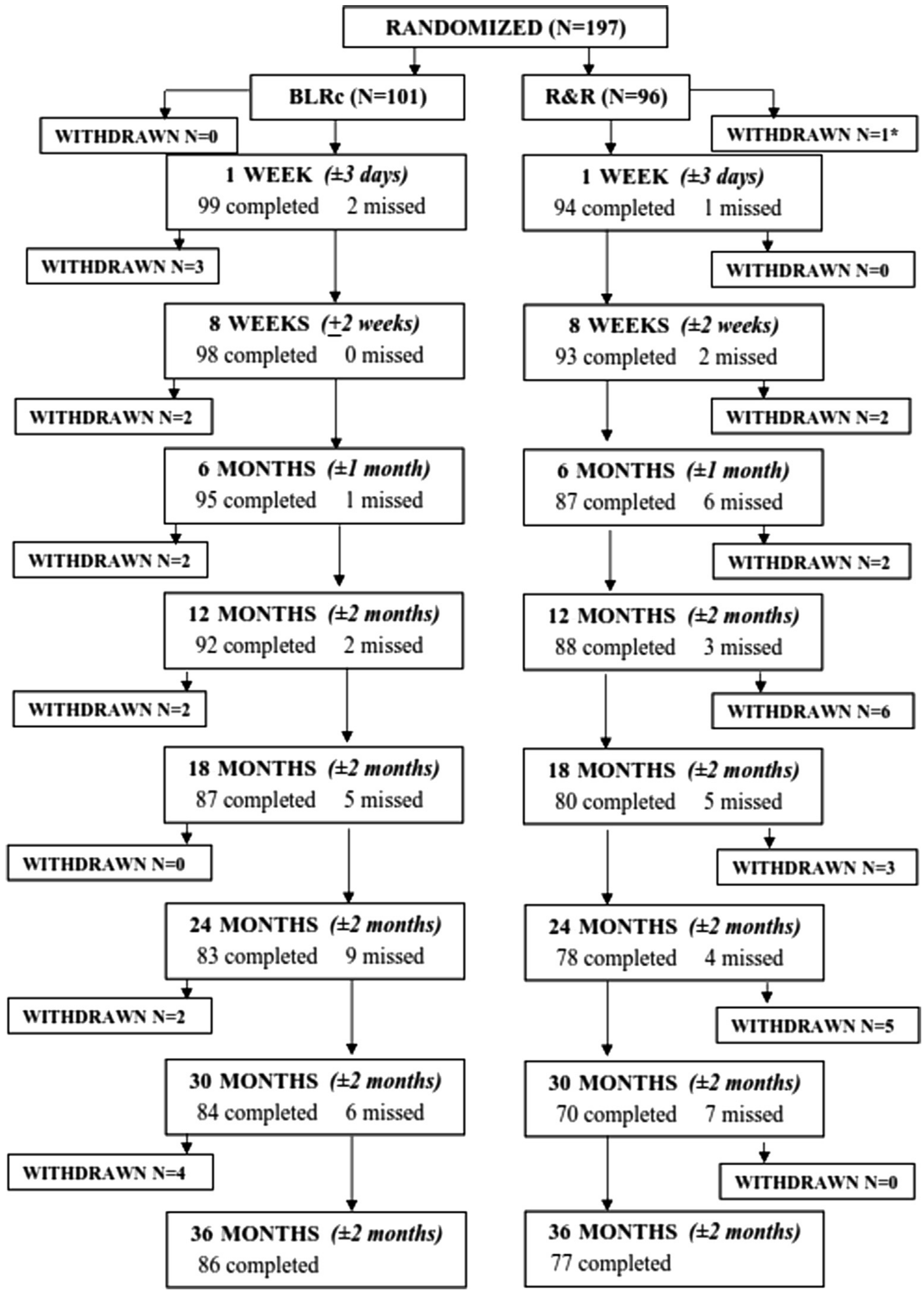


Figure 1. Flowchart showing progress of participants through study. *One participant in the R&R group was withdrawn from the study without undergoing surgery. BLRc = bilateral lateral rectus muscle recession; R&R = unilateral lateral rectus recession combined with medial rectus resection in the same eye.

122 (62%) were female, and 113 (57%) were white. The mean preoperative angle (largest at distance, near, or remote distance) was 28±6 PD. Baseline demographic and clinical characteristics appeared similar for both treatment groups (Tables 5–7).

Surgical Complications

There were no intraoperative complications reported in either group. Postoperative complications were reported at the 1-week or 8-week visits in 0 participants in the BLRc group and in 3 participants in the R&R group (1 each of small epithelial cyst, dell, and conjunctival edema overlying medial rectus resection site), none of which was serious and all of which resolved without sequelae.

Visit Completion

In the BLRc and R&R groups, 88% (89 of 101) and 84% (81 of 96) of participants, respectively, contributed to the primary outcome

Table 5. Baseline Demographic and Clinical Characteristics by Treatment Group (n = 197)*

Characteristic	BLRc No.	BLRc %	R&R No.	R&R %
All	101	100	96	100
Gender				
Female	64	63	58	60
Male	37	37	38	40
Race/ethnicity				
White	58	57	55	57
Black	13	13	14	15
Hispanic	19	19	25	26
Other	11	11	2	2
Age at randomization (yrs)				
3−<4	14	14	15	16
4−<5	19	19	24	25
5−<6	14	14	20	21
6−<7	15	15	10	10
7−<8	15	15	11	11
8−<9	10	10	4	4
9−<10	9	9	10	10
10−<11	5	5	2	2
Mean (SD)	6.4 (2.1)		5.9 (1.9)	
Prior nonsurgical treatment				
No treatment	49	49	49	51
Patching alone	36	36	29	30
Overminus spectacles alone	6	6	4	4
Vision therapy alone	2	2	3	3
Combination or other	8	8	11	11
Randot Preschool near stereoacuity (arcsec)[†]				
40	15 (15)		16 (17)	
60	22 (22)		20 (21)	
100	28 (28)		31 (32)	
200	12 (12)		13 (14)	
400	24 (24)		16 (17)	
Mean (SD) (log arcsec)	2.1 (0.4)		2.0 (0.3)	
Range (log arcsec)	1.6−2.6		1.6−2.6	
Distance Randot stereoacuity (arcsec)				
60	27 (27)		25 (27)	
100	14 (14)		19 (20)	
200	18 (18)		16 (17)	
400	20 (20)		13 (14)	
Nil	20 (20)		20 (22)	
Mean (SD) (log arcsec)	2.3 (0.4)		2.3 (0.4)	
Range (log arcsec)	1.8−2.9		1.8−2.9	

arcsec = seconds of arc; BLRc = bilateral lateral rectus recession; R&R = unilateral lateral rectus recession combined with medial rectus resection in the same eye; SD = standard deviation.
*Percentages for each factor may not total 100% exactly because of rounding.
[†]Participants were required to have 400 arcsec or better of near stereoacuity at enrollment.

analysis by either completing the 3-year visit or by meeting suboptimal surgical outcome criteria before the 3-year visit (Fig 1). There did not seem to be any meaningful baseline differences between those completing the 3-year visit and those who did not (Table 8).

Postoperative Nonsurgical Treatment

Postoperative nonsurgical treatment was prescribed for exotropia, esotropia, diplopia, or a combination thereof in 18 (18%) BLRc and 36 (38%) R&R group participants (Table S9, available at www.aaojournal.org). Orthoptic exercises (alone or with other treatments) were prescribed for 6 (6%) and 8 (8%) participants in the BLRc and R&R groups, respectively ($P = 0.53$); patching (alone or with other treatments) was prescribed for 4 (4%) and 25 (26%) participants in the BLRc and R&R groups, respectively ($P < 0.001$). Over the 3 years, 11 (11%), 6 (6%), and 1 (<1%) participants in the BLRc group and 10 (10%), 23 (24%), and 3 (3%) participants in the R&R group were prescribed nonsurgical treatment for exodeviation, for esodeviation, or for both exodeviation and esodeviation, respectively.

Primary Outcome: Suboptimal Surgical Outcome by 3 Years

Suboptimal surgical outcome by 3 years (at a masked examination between 6 months and 3 years after surgery or reoperation at any

Table 6. Baseline Ocular Alignment by Treatment Group

Baseline Exotropia Magnitude by Prism and Alternate Cover Test (PD)	Distance				Near				Remote Distance				Largest Angle by Remote Distance, Distance, or Near*			
	BLRc (n = 101)		*R&R (n = 96)*		*BLRc (n = 101)*		*R&R (n = 96)*		*BLRc (n = 101)*		*R&R (n = 96)*		*BLRc (n = 101)*		*R&R (n = 96)*	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
10–14	0	0	0	0	10	10	12	13	0	0	1	1	0	0	0	0
15–18	12	12	7	7	16	16	15	16	9	9	5	5	7	7	4	4
20–25	55	54	50	52	38	38	33	34	45	45	41	43	50	50	45	47
30–35	29	29	38	40	31	31	34	35	38	38	45	47	35	35	43	45
40	5	5	1	1	6	6	2	2	9	9	4	4	9	9	4	4
Mean (SD)	26 (6)		26 (6)		25 (8)		24 (8)		28 (6)		27 (6)		28 (6)		27 (6)	
Range	16–40		16–40		10–40		10–40		16–40		14–40		18–40		18–40	

BLRc = bilateral lateral rectus recession; PD = prism diopter; R&R = unilateral lateral rectus recession combined with medial rectus resection in the same eye; SD = standard deviation.
*Surgical dose was based on the largest angle at remote distance, distance, or near.

Table 7. Baseline Exotropia Control by Treatment Group

Baseline Exotropia Control (in Points)	Distance				Near			
	BLRc (n = 101)		*R&R (n = 96)*		*BLRc (n = 101)*		*R&R (n = 96)*	
	No.	%	No.	%	No.	%	No.	%
(0) No exotropia unless dissociated, recovers <1 seconds (phoria)	1	<1	0	0	10	10	20	21
(1) No exotropia unless dissociated, recovers 1–5 seconds	9	9	6	6	36	36	27	28
(2) No exotropia unless dissociated, recovers >5 seconds	19	19	19	20	19	19	19	20
(3) Exotropia <50% of 30-second observation	23	23	19	20	24	24	18	19
(4) Exotropia >50% of 30-second observation	18	18	31	32	11	11	12	13
(5) Constant exotropia	31	31	21	22	1	<1	0	0
Mean (SD)	3.4 (1.4)		3.4 (1.2)		1.9 (1.2)		1.7 (1.3)	
Range	0–5		1–5		0–5		0–4	

BLRc = bilateral lateral rectus recession; R&R = unilateral lateral rectus recession combined with medial rectus resection in the same eye; SD = standard deviation.

Table 8. Clinical Characteristics According to Study Completion

Clinical Characteristics	Participants Withdrawn from Study (n = 34)		Participants Completing 3-Year Visit (n = 163)	
	BLRc (n = 15)	*R&R (n = 19)*	*BLRc (n = 86)*	*R&R (n = 77)*
Baseline age	6.6	5.6	6.3	6.0
Baseline stereo (log arcsec)	2.2	2.0	2.0	2.0
Baseline control at distance (points)	2.7	3.4	3.5	3.5
Baseline control at near (points)	1.8	1.9	2.0	1.7
Baseline PACT at distance (PD)	26	23	26	27
Baseline PACT at near (PD)	25	20	25	25
Previous nonsurgical treatment, no. (%)	4 (27)	8 (42)	48 (56)	39 (51)
Preoperative surgical exodeviation (PD)	27	24	28	28
Last follow-up visit control at distance (points)	1.0	1.6	1.2	1.0
Last follow-up visit PACT at distance (PD)	−1	6*	10	9

arcsec = seconds of arc; BLRc = bilateral lateral rectus recession; PACT = prism and alternate cover test; PD = prism diopter; R&R = unilateral lateral rectus recession combined with medial rectus resection in the same eye.
*Distance PACT is missing at the last completed visit for one R&R group participant who was withdrawn from the study.

time) occurred in 43 of 101 participants in the BLRc group and in 33 of 96 participants in the R&R group. The cumulative probability of suboptimal surgical outcome by 3 years was 46% in the BLRc group compared with 37% in the R&R group (treatment group difference of BLRc minus R&R, 9%; 95% CI, −6% to 23%; Fig 2; Table 10). In both treatment groups, the first suboptimal surgical outcome criterion that was met most often was residual or recurrent exotropia (29 of 43 [67%] in the BLRc group and 21 of 33 [64%] in the R&R group).

Reoperation by 3 Years

A reoperation was performed by 3 years in 9 participants (10%) in the BLRc group (8 of 9 met suboptimal surgical outcome criteria) and in 4 participants (5%) in the R&R group (3 of 4 met suboptimal surgical outcome criteria; treatment group difference of BLRc minus R&R, 5%; 95% CI, −2% to 13%); reasons for reoperation are listed in Figure 3.

Suboptimal Surgical Outcome at the 3-Year Visit

Among participants who completed the 3-year visit, 29% (25 of 86) in the BLRc group and 17% (13 of 77) in the R&R group met suboptimal surgical outcome criteria at the time of the 3-year visit (regardless of whether criteria were met at any previous visits) or had undergone reoperation (treatment group difference of BLRc minus R&R, 12%; 95% CI, −1% to 25%).

Among the 38 BLRc group participants who met suboptimal surgical outcome criteria before 3 years and returned for the 3-year visit, 8 had undergone reoperation, 15 met the suboptimal surgical outcome criteria at 3 years, 5 met criteria for complete or near-complete resolution, and 10 met neither (Table S11a, available at www.aaojournal.org). Among the 26 R&R group participants who met suboptimal surgical outcome criteria before 3 years and returned for the 3-year visit, 4 had undergone reoperation, 7 met suboptimal surgical outcome criteria at 3 years, 7 met criteria for complete or near-complete resolution, and 9 met neither (Table S11b, available at www.aaojournal.org). Among the participants with suboptimal surgical outcomes identified before 3 years and who had not undergone reoperation, the proportion who no longer met suboptimal surgical outcome criteria at the 3-year visit was 50% (15 of 30) in the BLRc group compared with 70% (16 of 23) in the R&R group ($P = 0.17$).

Complete or Near-Complete Resolution

Among participants who completed the 3-year visit, criteria for complete or near-complete resolution at the 3-year visit were met by 30% (26 of 86) in the BLRc group and 45% (35 of 77) in the R&R group at the 3-year visit (treatment group difference of BLRc minus R&R, −15%; 95% CI, −30% to −0.0003% favoring the R&R group). The proportions of patients who met complete or near-complete resolution at 3 years and never met suboptimal surgical outcome criteria were 24% (21 of 86) in the BLRc group and 36% (28 of 77) in the R&R group (treatment group difference of BLRc minus R&R, −12%; 95% CI, −26% to 3%).

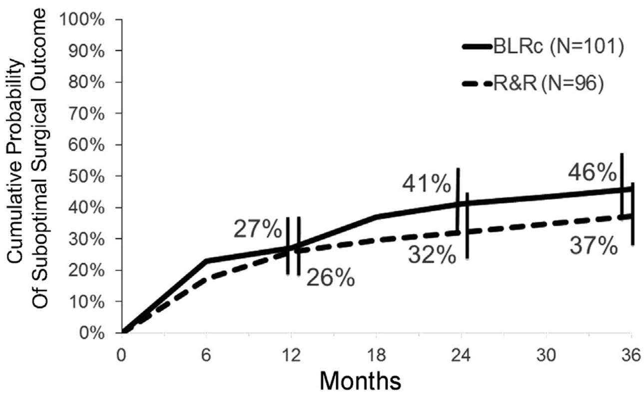
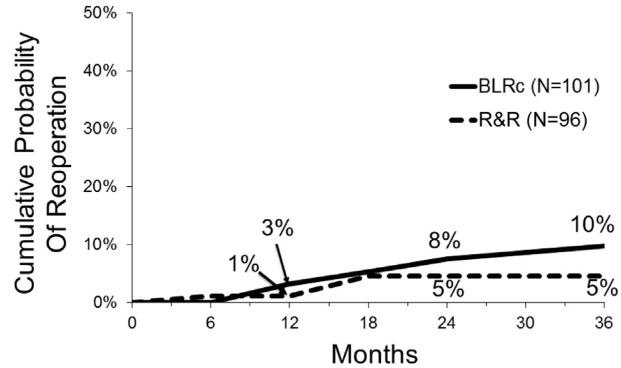


Figure 2. Graph showing cumulative probability of suboptimal surgical outcome by 3 years from Kaplan-Meier analysis (n = 197). Treatment group difference of bilateral lateral rectus muscle recession (BLRc) minus unilateral lateral rectus recession combined with a medial rectus resection in same eye (R&R), 9% (95% confidence interval, −6% to 23%). Vertical error bars indicate 95% confidence intervals.

Table 10. Suboptimal Surgical Outcome by 3 Years (n = 197)

	6 Months		12 Months		18 Months		24 Months		30 Months		36 Months		Total	
	BLRc	*R&R*	*BLRc*	*R&R*	*BLRc*	*R&R*	*BLRc*	*R&R*	*BLRc*	*R&R*	*BLRc*	*R&R*	*BLRc*	*R&R*
No. at risk	96	93	71	75	66	61	58	57	53	52	48	50	N/A	N/A
No. with suboptimal surgical outcome	23	16	3	8	9	3	4	2	2	2	2	2	43	33
XT	14	7	3	5	6	3	3	2	1	2	2	2	29	21
Constant ET	1	1		1									1	2
Stereo loss	4	4			3		1		1				9	4
Stereo loss and XT	1												1	0
Stereo loss and constant ET	2	3		2									2	5
Reoperated without meeting suboptimal surgical outcome	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Cumulative probability of meeting suboptimal surgical outcome (%)	24	17	27	26	37	30	41	32	44	35	46	37	N/A	N/A

BLRc = bilateral lateral rectus recession; Constant ET = constant esotropia ≥6 prism diopters by simultaneous prism and cover test at distance or near, confirmed by a retest; N/A = not applicable; R&R = unilateral lateral rectus recession combined with medial rectus resection in the same eye; Stereo loss = decrease in Randot Preschool Stereotest near stereoacuity ≥2 octaves (≥0.6 log seconds of arc) from enrollment, or to nil, confirmed by a retest; XT = exotropia ≥10 prism diopters by simultaneous prism and cover test at distance or near, confirmed by a retest.



Reasons for Reoperation by 3 Years	BLRc (N=9)	R&R (N=4)
XT	1	1
XT and worsening stereo	2	
XT, worsening stereo and social concerns	1	
XT, diplopia, and headaches	1	
XT and squinting with one eye closed	1	
ET	1	1
ET, worsening stereo, and diplopia	1	
ET, worsening stereo and social concerns		1
ET, worsening stereo, social concerns, and amblyopia		1
Inferior oblique overaction	1	

Figure 3. Graph showing reoperation by 3 years (n = 197). BLRc = bilateral lateral rectus muscle recession; ET = esotropia; R&R = unilateral lateral rectus recession combined with medial rectus resection in the same eye; XT = exotropia.

Constant Esotropia Suboptimal Surgical Outcome

The cumulative probability of constant esotropia of 6 PD or more at distance, at near, or both at any examination from 6 months through 3 years was 3% in the BLRc group and 10% in the R&R group (treatment group difference of BLRc minus R&R, −7%; 95% CI, −14% to 0.23%; Table 12). In both treatment groups, 67% of participants who met the constant esotropia suboptimal surgical outcome were prescribed nonsurgical treatment (2 of 3 in the BLRc group and 6 of 9 in the R&R group). Among participants who had constant esotropia who did not undergo reoperation and completed the 3-year visit, constant esotropia of 6 PD or more at distance, at near, or both was no longer present in 1 of 2 in the BLRc group versus 7 of 7 in the R&R group.

Exotropia Suboptimal Surgical Outcome

The cumulative probability of having exotropia of 10 PD or more at distance, near, or both at any examination from 6 months through 3 years was 34% in the BLRc group and 26% in the R&R group (treatment group difference of BLRc minus R&R, 8%; 95% CI, −6% to 21%; Table 12). Of these patients, 23% (7 of 31) underwent reoperation in the BLRc group versus 5% (1 of 22) in the R&R group. Among participants with residual exotropia who did not undergo reoperation and completed the 3-year visit, exotropia of 10 PD or more at distance, near, or both was no longer present in 9 of 20 (45%) in the BLRc group versus 8 of 15 (53%) in the R&R group.

Table 12. Suboptimal Surgical Outcomes by 3 Years (Primary Outcome) and Cause-Specific Outcomes by 3 Years (Secondary)

	BLRc Group		R&R Group			
Outcome	*No. with Outcome*	*Kaplan-Meier Cumulative Probability (%)*	*No. with Outcome*	*Kaplan-Meier Cumulative Probability (%)*	Treatment Group Difference (%; 95% Confidence Interval)*	P Value
Suboptimal surgical outcome by 3 yrs	43	46	33	37	9 (−6 to 23)	0.24
XT by 3 yrs†	31	34	22	26	8 (−6 to 21)	0.25
Constant ET by 3 yrs†	3	3	9	10	−7 (−14 to 0.23)	0.06
Stereo loss by 3 yrs†	13	14	9	10	4 (−5 to 14)	0.36

BLR = bilateral lateral rectus recession; Constant ET = constant esotropia ≥6 prism diopters by simultaneous prism and cover test at distance or near, confirmed by a retest; R&R = unilateral lateral rectus recession combined with medial rectus resection in the same eye; stereo loss = decrease in Randot Preschool Stereotest near stereoacuity ≥2 octaves (≥0.6 log seconds of arc) from enrollment, or to nil, confirmed by a retest; XT = exotropia ≥10 prism diopters by simultaneous prism and cover test at distance or near, confirmed by a retest.
*Treatment group differences are calculated as bilateral lateral rectus recession minus unilateral lateral rectus recession combined with medial rectus resection in the same eye, so positive differences favor the unilateral lateral rectus recession combined with medial rectus resection in the same eye group.
†Cause-specific criteria (XT, constant ET, stereo loss) refer to meeting the given criteria by 3 yrs, before any reoperation, and regardless of whether suboptimal surgical outcome was met by another criteria.

Change in Exotropia Control, Prism and Alternate Cover Test Magnitude, and Stereoacuity over 3 Years

In the BLRc and R&R groups, the proportions of participants with distance exotropia control of 2 or better at the 3-year visit were 29% (29 of 101) and 26% (25 of 96), respectively, at baseline and 81% (70 of 86) and 85% (64 of 77), respectively, at the 3-year visit. Mean improvement in exotropia control over 3 years was 2.3 versus 2.5 points at distance ($P = 0.44$) and 1.3 versus 1.1 points at near ($P = 0.64$) for the BLRc and R&R groups, respectively (Table 13; Fig 4). The mean reduction in PACT magnitude over 3 years was 16 PD versus 18 PD at distance ($P = 0.21$) and 15 PD versus 16 PD at near ($P = 0.38$; Table 13; Fig 4). In both treatment groups, mean improvement in stereoacuity at 3 years was 0.1 log seconds of arc at distance ($P = 0.82$) and 0.2 log seconds of arc at near ($P = 0.93$; Table S14, available at www.aaojournal.org).

Health-Related Quality of Life

There were no significant differences between the BLRc and R&R treatment groups in the distribution of 3-year IXTQ scores as assessed by the child IXTQ (participants 5 to 7 years of age at the 3-year follow-up: median, 91 vs. 86 [$P = 0.30$]; participants 8 to 13 years of age at the 3-year follow-up: median, 82 vs. 82 [$P = 0.77$]), the parent proxy IXTQ (median, 86 vs. 91; $P = 0.51$), and the parent psychosocial (median, 97 vs. 100; $P = 0.42$), parent function (median, 83 vs. 86; $P = 0.68$), and parent surgery (median, 83 vs. 92; $P = 0.64$) subscales of the parent version of the IXTQ.

Discussion

In this randomized trial, we compared BLRc and R&R in 197 children with basic IXT who were 3 to younger than 11 years of age. We found the cumulative probability of a suboptimal surgical outcome through 3 years of follow-up was 46% in the BLRc group and 37% in the R&R group, a difference of 9% in favor of the R&R group (95% CI, −6% to 23%). Although the difference was not statistically significant, the CI reasonably rules out a moderately sized benefit in favor of BLRc, but cannot rule out the possibility of a moderately sized benefit in favor of R&R.

We also compared several secondary outcome measures. The first was the rate of suboptimal surgical outcome at the 3-year masked examination, ignoring the results from the earlier masked examinations. This analysis was performed to account for surgical overcorrections that improved spontaneously before the 3-year visit. The rates of suboptimal surgical outcome at 3 years did not differ statistically, nor did the reoperation rates differ between groups. However, it is noteworthy that 6 of 9 reoperations in the BLRc group were for recurrent exotropia, whereas 3 of the 4 reoperations in the R&R group were for esotropia. Both procedures improved mean control score and reduced deviation magnitude similarly. Because a post hoc outcome of complete or near-complete resolution at 3 years favored the R&R procedure (45% in the R&R group vs. 30% in the BLRc group), and because suboptimal surgical outcomes during the 3 years and at the end of 3 years and rates of reoperation were in the direction of favoring R&R but were not statistically significant, there may be slightly more support for the R&R procedure than for BLRc. However, because these outcomes are correlated with each other, we might expect them all to favor the same procedure, regardless of whether the overall results of our particular study reflect the underlying truth in the population of interest.

Our study used a standard dose of surgery for each group. Differing amounts of surgery may have produced different results. Using a greater amount of recession than we used for bilateral lateral rectus muscle recessions (augmenting) has been advocated.[12] Although augmented recession may decrease failure rates resulting from residual exotropia, it may do so at the expense of increasing failure rates resulting from overcorrection.

Kushner[13] reported the only other prospective randomized clinical trial comparing these 2 procedures, with a follow-up period ranging from 12 to 15 months. He found that 82% of 17 patients who underwent R&R achieved a successful outcome, compared with only 52% of 19 patients who underwent BLRc ($P < 0.05$).[13] His definition of a satisfactory outcome was alignment ranging between 0 and 5 PD of esophoria and 0 and 10 PD of exophoria. In addition, any intermittent or

Table 13. Three-Year Exotropia Control and Ocular Alignment (n = 163)

	Distance		Near	
	BLRc (n = 86)	*R&R (n = 77)*	*BLRc (n = 86)*	*R&R (n = 77)*
	No. (%)	*No. (%)*	*No. (%)*	*No. (%)*
Exotropia control*				
At 3 yrs				
Not applicable (no exodeviation)	19 (22)	25 (32)	20 (23)	21 (27)
(0) No exotropia unless dissociated, recovers <1 seconds (phoria)	25 (29)	22 (29)	36 (42)	32 (42)
(1) No exotropia unless dissociated, recovers 1−5 seconds	14 (16)	11 (14)	16 (19)	13 (17)
(2) No exotropia unless dissociated, recovers >5 seconds	12 (14)	6 (8)	6 (7)	4 (5)
(3) Exotropia <50% of 30-second observation	5 (6)	4 (5)	1 (1)	4 (5)
(4) Exotropia >50% of 30-second observation	6 (7)	4 (5)	6 (7)	3 (4)
(5) Constant exotropia	5 (6)	5 (6)	1 (1)	0 (0)
Mean (SD)	1.2 (1.6)	1.0 (1.6)	0.7 (1.2)	0.6 (1.1)
Range	0−5	0−5	0−5	0−4
Change between baseline and 3 yrs†				
Mean (SD)	2.3 (1.7)	2.5 (1.7)	1.3 (1.6)	1.1 (1.6)
Range	−3 to 5	−2 to 5	−3 to 4	−3 to 4
Prism and alternate cover test*				
At 3 yrs (PD)				
No deviation	10 (12)	21 (27)	11 (13)	15 (19)
1−9 exodeviation	23 (27)	17 (22)	21 (24)	24 (31)
10−14 exodeviation	15 (17)	12 (16)	16 (19)	9 (12)
15−18 exodeviation	10 (12)	7 (9)	11 (13)	5 (6)
20−25 exodeviation	16 (19)	12 (16)	13 (15)	14 (18)
30−35 exodeviation	3 (3)	2 (3)	3 (3)	3 (4)
40−45 exodeviation	0	0	1 (1)	0
10−14 esodeviation	2 (2)	0	1 (1)	0
1−9 esodeviation	7 (8)	6 (8)	9 (10)	7 (9)
Mean (SD)	10 (10)	9 (10)	10 (11)	9 (10)
Range	−14 to 35	−6 to 30	−14 to 40	−6 to 30
Change between baseline and 3 yrs†				
Mean (SD)	16 (11)	18 (10)	15 (12)	16 (12)
Range	−10 to 44	−5 to 36	−14 to 40	−12 to 41

BLRc = bilateral lateral rectus recession; PD = prism diopters; R&R = unilateral lateral rectus recession combined with medial rectus resection in the same eye; SD = standard deviation.

*For treatment group comparisons of mean 3-yr control using linear regression models adjusting for baseline control, $P = 0.44$ and $P = 0.64$ for distance and near control, respectively. For treatment group comparisons of mean 3-year prism and alternate cover test using linear regression models adjusting for baseline prism and alternate cover test, $P = 0.21$ and $P = 0.38$ for distance and near prism and alternate cover test, respectively.

†Change is defined as the baseline value minus the 3-year value; therefore, positive change equals improvement. If the 3-year prism and alternate cover test is an esodeviation, then change in prism and alternate cover test from baseline is the reduction in the exodeviation plus the amount of the 3-year exodeviation.

constant esotropia or exotropia was considered an unsatisfactory outcome, as was any reoperation, prism treatment after surgery, or adjustment of spectacle power to alter alignment. Although our primary outcome measure differs in many ways from that of Kushner, the results of the 2 studies are not entirely inconsistent because our study could not rule out a moderate benefit of R&R.

Only a small number of our participants demonstrated constant esotropia at or after the 6-month follow-up examination, and nearly all of those who did not undergo reoperation showed spontaneous resolution (1 of 2 patients in the BLRc group and 7 of 7 patients in the R&R group). The resulting 11% (1 of 9) observed rate of initial overcorrections that were longstanding (i.e., at 3 years) is substantially lower than that reported by Buck et al,[14] who found that among initial surgical overcorrections, defined as any manifest esotropia at distance or near, 40% (10 of 25) remained at 2 years. However, direct comparison with our study is difficult because of differences in surgical doses and follow-up periods and the lack of randomization in the Buck et al study.

The strengths of this study include the large sample size, the relatively long follow-up, a predefined masked outcome measure, and its multicenter design. Our study also has several limitations. Our secondary outcome analyses (suboptimal surgical outcome at 3 years, reoperation, and complete or near-complete resolution) were all subject to investigator bias, because reoperation was at investigator discretion as soon as suboptimal surgical outcome criteria were met and because the previous type of surgical procedure might have impacted the decision to reoperate. An

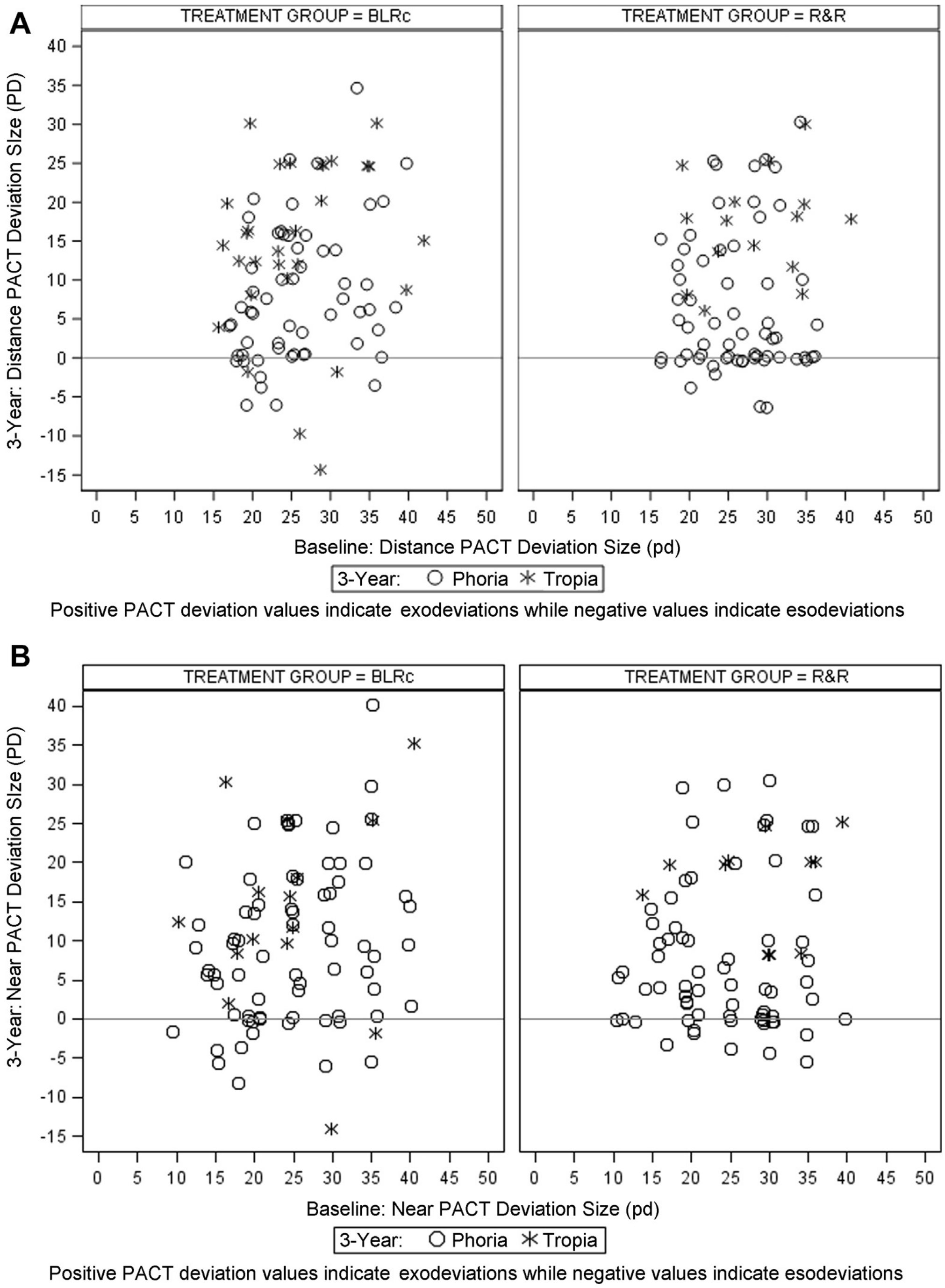


Figure 4. Scatterplots showing baseline versus 3-year prism and alternate cover test (PACT) magnitude (n = 86 for bilateral lateral rectus muscle recession [BLRc] and 77 for unilateral lateral rectus recession combined with medial rectus resection in the same eye [R&R]) for (**A**) distance and (**B**) near deviations. A deviation is defined as a tropia (X) if a tropia was present by cover-and-uncover test at 3 years; otherwise, it was defined as phoria (O).

additional limitation of our secondary outcomes was that complete or near-complete resolution and the cause-specific suboptimal surgical outcomes were defined post hoc. Another limitation of the 3 cause-specific suboptimal surgical outcomes by 3 years is their nonindependence, because reoperation is a competing risk for each. The low overall rate of reoperation minimizes the impact of this lack of independence; however, because participants in the BLRc group were slightly more likely to be censored because of reoperation, we may have slightly underestimated the outcome rates in this group.

We did not find a statistically significant difference in the suboptimal surgical outcome rate by 3 years between children treated with BLRc compared with those treated with R&R. Our results reasonably rule out a moderately sized benefit in favor of BLRc, but cannot rule out the possibility of a moderately sized benefit in favor of R&R. Nevertheless, based on our findings, we are unable to recommend one surgical approach over the other. Although the 3-year postoperative results reported here were obtained from more than 80% of enrolled participants and represent the longest-term follow-up for a prospective randomized cohort of children with IXT who underwent surgery, 3 years of follow-up is a relatively short period for assessing treatment of IXT. Accordingly, an extension study has begun that will follow up these children for an additional 5 years.

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HUMAN SUBJECTS: Human subjects were included in this study. The study was conducted according to the tenets of the Declaration of Helsinki by the Pediatric Eye Disease Investigator Group (PEDIG) at academic and community based clinical sites. The protocol and Health Insurance Portability and Accountability Act (HIPAA)−compliant informed consent forms were approved by institutional review boards, and a parent or guardian of each study participant gave written informed consent. An independent data and safety monitoring committee provided study oversight.

No animal subjects were included in this study.

Author Contributions:

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Abbreviations and Acronyms:
BLRc = bilateral lateral rectus recession; **CI** = confidence interval; **D** = diopter; **HRQOL** = health-related quality of life; **IXT** = intermittent exotropia; **IXTQ** = Intermittent Exotropia Questionnaire; **PACT** = prism and alternate cover test; **PD** = prism diopter; **R&R** = unilateral lateral rectus recession combined with medial rectus resection in the same eye; **SPCT** = simultaneous prism and cover test.

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8-Year Outcomes of Bilateral Lateral Rectus Recessions versus Unilateral Recess-Resect in Childhood Basic-Type Intermittent Exotropia

The Pediatric Eye Disease Investigator Group*

Abstract

Objective: To report 8-year outcomes from a randomized controlled trial (RCT) comparing bilateral lateral rectus muscle recessions (BLRc) with unilateral recess-resect (R&R) for childhood intermittent exotropia (IXT).

Design: Eight-year follow-up of RCT cohort

Participants: 123 of 197 randomized participants agreed to continue follow-up after the 3-year outcome visit (baseline age 3 to <11 years with basic-type IXT 15-40 prism diopters (Δ) by prism and alternate cover test (PACT), baseline stereoacuity of 400 arcsec or better, no prior surgery)

Methods: Following the RCT primary outcome at 3 years, annual follow-up from 4 through 8 years with treatment at investigator discretion.

Main Outcome Measures: Suboptimal surgical outcome by 8 years after randomization, defined as any of the following at any visit: exotropia ≥10Δ by simultaneous prism cover test (SPCT) at distance or near; constant esotropia (ET) ≥6Δ by SPCT at distance or near; loss of near stereoacuity by ≥0.6 log arcsec from baseline; or reoperation. Secondary outcomes included 1) reoperation by 8 years and 2) complete or near-complete resolution at 8 years: exodeviation <10Δ by SPCT and PACT at distance and near *and* ≥10Δ reduction from baseline PACT at distance and near; ET <6Δ at distance and near; no decrease in stereoacuity by ≥0.6 log arcsec from baseline; no reoperation or nonsurgical treatment for IXT.

Results: The Kaplan-Meier cumulative probability of suboptimal surgical outcome through 8 years was 68% (55 events among 101 at risk) for BLRc and 53% (42 events among 96 at risk) for R&R (difference = 15%, 95% CI: −2% to 32%, P = 0.08). Complete or near-complete resolution at 8 years occurred in 14% (6/42) for BLRc and 37% (16/43) for R&R (difference = −22%, 95% CI: −44% to −0.1%, P = 0.049). The cumulative probability of reoperation was 30% for BLRc and 11% for R&R (difference = 19%, 95% CI=2% to 36%, P = 0.049).

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- American Association for Pediatric Ophthalmology and Strabismus Annual Meeting, New York City, New York, April 1, 2023. (Oral Presentation)

Conclusions: Despite no significant difference at primary outcome, the 95% CI did not exclude a moderate benefit of R&R, which together with secondary outcomes, suggests that unilateral R&R followed by usual care may yield better long-term outcomes than BLRc followed by usual care, for basic-type childhood IXT, using our surgical doses.

Precis:

Over eight years following surgery and usual care, differences in suboptimal outcomes for recess-resect versus bilateral recessions for childhood intermittent exotropia were not statistically significant, but secondary outcomes suggested benefit of recess-resect.

Intermittent exotropia (IXT) is a common form of childhood-onset strabismus[1] for which surgical correction is often performed.[2-4] One unresolved question is whether post-operative outcomes differ with bilateral lateral rectus recessions (BLRc) versus unilateral lateral rectus muscle recession with medial rectus muscle resection (R&R). We previously reported the results of an RCT[5] comparing BLRc and R&R procedures for basic type IXT in children 3 to <11 years old, in which we found no statistically significant difference in sub-optimal outcome by 3 years postoperatively (46% in BLRc and 37% in R&R; difference = 9%; 95% confidence interval (CI): −6% to 23%).[5] We are aware of three other RCTs that have addressed this question. Both Kushner[6] and Somer et al[7] reported higher success rates at one year after surgery with R&R vs. BLRc, whereas Zhang et al[8] reported that both groups had similar success rates over the same period. Given the propensity of IXT to recur over time,[9,10] longer-term effectiveness of surgical approaches should also be evaluated. The purpose of the present study was to evaluate long-term outcomes 8 years after surgery in the PEDIG RCT for which 3-year outcomes have been previously reported.[5]

Methods

The study was funded by the National Eye Institute of the National Institutes of Health and conducted according to the tenets of the Declaration of Helsinki by the Pediatric Eye Disease Investigator Group (PEDIG) at 35 academic and community-based clinical sites. The protocol and Health Insurance Portability and Accountability Act (HIPAA)-compliant informed consent forms were approved by institutional review boards for each site, and a parent or guardian of each study participant gave written informed consent. The study is listed on www.clinicaltrials.gov (clinicalcaltrials.gov identifier: NCT01032603);[11] the full protocol is available at www.pedig.net (accessed 2/6/23).

Original 3-year Randomized Controlled Trial

We enrolled 197 children, age 3 to <11 years, with basic-type IXT, 15 to 40Δ (largest deviation at near, distance, or remote distance) by prism and alternate cover test (PACT), and near stereoacuity of at least 400 arc-seconds using the Randot® Preschool Stereoacuity test (Stereo Optical Co., Inc., Chicago, IL). Participants were randomly assigned to one of two surgical procedures: BLRc or R&R. Follow-up visits occurred every six months after surgery for 3 years. Reoperation was permitted only after suboptimal surgical outcome criteria were met and confirmed by a retest. Additional details of the protocol and results have been published previously.[5,12]

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4 to 8-Years Post-Randomized Trial Follow-up (Extension Study)

The extension study (4-to-8-year follow-up) was implemented in February 2015. The parent or guardian for each randomized participant was asked to reconsent to extended follow-up, regardless of whether they were still active, had completed, or had withdrawn from the 3-year RCT. Participants who consented to the extension study had follow-up visits at 4, 5, 6, 7, and 8 years (±2 months) from randomization. At each follow-up visit, an examiner masked to the participant's treatment group measured near stereoacuity using the Randot® Preschool Stereoacuity test, exotropia control using the IXT Office Control Scale [13,14] (Table S1) (mean of 3 measures [beginning, middle, and end of the masked exam) at distance and near, cover-uncover test, simultaneous prism and cover test (SPCT), and PACT at distance and near. At the 8-year visit, the Intermittent Exotropia Questionnaire (IXTQ) was administered to the child and parent to measure IXT-related quality of life and the Diplopia Questionnaire[15] was administered to the child to assess the presence and frequency of diplopia in specific gaze positions.

Statistical Methods

In parallel with the previously reported 3-year outcomes, the primary outcome for the current analysis was suboptimal surgical outcome by 8 years was defined as any of the following at any follow-up examination from 6 months to 8 years: 1) $\geq 10\Delta$ exotropia by SPCT at distance or near; 2) constant esotropia of $\geq 6\Delta$ by SPCT; 3) loss of ≥ 0.6 log arcsec stereoacuity compared with baseline; or 4) reoperation without meeting any other criteria. Suboptimal surgical outcome had to be confirmed by a retest during the 3-year RCT; however, retesting was not performed during the 4-to-8-year follow-up to streamline visits and reduce participant testing burden.

For the primary analysis, the cumulative proportion of participants meeting criteria for suboptimal surgical outcome by 8 years was obtained using the Kaplan-Meier method and compared between treatment groups using the Z test. Assessment of suboptimal surgical outcome by 8 years included all participants originally enrolled in the RCT regardless of their participation in the extension study. Data for participants who did not meet suboptimal surgical outcome criteria were censored at the time of their last completed study visit.

Several secondary outcomes were analyzed. The cumulative proportion of reoperation by 8 years was compared between treatment groups using the same statistical methods used for the primary analysis. Additional secondary analyses were treatment group comparisons of outcomes at the 8-year visit (from participants who completed the 8-year visit within the analysis window of 7.5 to <9 years from randomization). At 8 years, the proportions of participants with: 1) suboptimal surgical outcome, 2) complete or near-complete resolution criteria, 3) spontaneous exotropia during the examination or average control score of 3 or higher at distance or near, and 4) a decrease in Randot Preschool stereoacuity of ≥ 0.6 log arcsec from enrollment, were compared between treatment groups using Barnard's unconditional exact test. Suboptimal surgical outcome at 8 years was defined as meeting any of the three suboptimal surgical outcome criteria at the 8-year follow-up visit (regardless of whether any criterion had been met at an earlier visit) or undergoing reoperation at any time before completing the 8-year visit. Complete or near-complete resolution at 8 years was

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defined as meeting all of the following at the 8-year visit: 1) exodeviation <10 Δ (tropia or phoria) by both SPCT and PACT at distance and near and ≥10 Δ reduction in PACT magnitude from both the distance and near angles at enrollment if the exodeviation was ≥10 Δ at baseline (and reduction to 0 if the exodeviation was <10 Δ at baseline), 2) esotropia <6 Δ at distance and near by SPCT, 3) no decrease in Randot Preschool stereoacuity of ≥0.6 log arcsec from the enrollment stereoacuity or to nil, 4) no reoperation or treatment with botulinum toxin, and 5) no non-surgical treatment for a recurrent or residual exodeviation. In addition, distance and near control, distance and near PACT, and Randot Preschool stereoacuity at the 8-year visit were compared between treatment groups using analysis of covariance (ANCOVA), adjusting for the corresponding measurement at enrollment. In the ANCOVA models, for the participants who underwent reoperation during the 8-year follow-up, their data at the last visit before reoperation were used for analyses. The type I error rate for all secondary outcomes was controlled using the adaptive false discovery rate (FDR)[16,17] approach to account for multiplicity, with the FDR controlled at the 5% probability level.

As exploratory analyses, we compared the mean Rasch-based HRQOL scores for the child IXTQ, each of the three parent IXTQ subscales, and the Diplopia Questionnaire scores[15] at 8 years between treatment groups using the Wilcoxon rank-sum test and Hodges-Lehmann estimator without adjustment for multiplicity.

All treatment-group differences were calculated as the BLRc group minus the R&R group. Analyses were conducted using SAS version 9.4 (SAS Institute Inc. Cary, NC).

Results

Baseline Characteristics

In the original 3-year RCT, 197 children were enrolled at 34 clinical sites with 101 assigned to the BLRc group and 96 assigned to the R&R (Figure 1); 123 (62%) elected to participate in the present extension study (64 from BLRc group and 59 from R&R group). In the BLRc and R&R groups, respectively, 46 (46% of 101 randomized; 72% of 64 enrolled in the extension) and 43 (45% of 96 randomized; 73% of 59 enrolled in the extension) of participants completed the 8-year visit. There did not appear to be meaningful differences in demographic and clinical characteristics at baseline between those who completed the 8-year visit and those who did not (either did not participate in the extension or were dropped during the extension) (Table S1).

Primary Outcome – Suboptimal Surgical Outcome by 8 Years

The Kaplan-Meier cumulative probability of suboptimal surgical outcome at any time point through 8 years was 68% (55 events among 101 at risk) in the BLRc group and 53% (42 events among 96 at risk) in the R&R group; the difference between BLRc and R&R was 15% (95% CI = −2% to 32%, P = 0.08) (Table 2, Figure 2). The most common reason for suboptimal surgical outcome was a residual or recurrent exotropia (34 of 55 [62%] in the BLRc group and 27 of 42 [64%] in the R&R group) (Table 2).

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Secondary Outcome – Reoperation by 8 Years

The cumulative probability of reoperation by 8 years was 30% (20 events among 101 at risk) with BLRc and 11% (7 events among 96 at risk) with R&R; the difference between BLRc and R&R was 19% (95% CI = 2% to 36%, P = 0.049) (Figure 3). Among participants who met suboptimal surgical outcome criteria, reoperation was performed for 30% (16 of 51) in the BLRc group and 14% (6 of 41) in the R&R group. In the BLRc group, 18 (90%) of 20 reoperations were for residual-recurrent exotropia, 1 (5%) was for consecutive esotropia, and 1 (5%) was for oblique muscle dysfunction; in the R&R group, 4 (57%) of 7 reoperations were for residual or recurrent exotropia and 3 (43%) were for consecutive esotropia.

Secondary Outcomes – Surgical Outcomes at the 8-Year Visit

Suboptimal surgical outcome at the 8-year visit was more likely with BLRc [48% (22 of 46)] than R&R [23% (10 of 43)] (difference = 25%; 95% CI = 0.2% to 50%, P = 0.049). Complete or near-complete resolution at the 8-year visit was less likely with BLRc [15% (7 of 46)] than with R&R [37% (16 of 43)] (difference = −22%; 95% CI = −44% to −0.1%, P = 0.049). Among participants completing the 8-year visit, reoperation was performed before 8 years in 14 of 46 (30%) in BLRc participants and 5 of 43 (12%) R&R participants. Most participants who had reoperation before the 8-year visit (13 of 14 in BLRc and 4 of 5 in R&R) also failed to meet at least one additional criterion for complete or near-complete resolution at 8 years.

Secondary Outcomes – Change in Exotropia Control PACT Magnitude, and Stereoacuity at 8 Years

The mean (standard deviation) distance exotropia control score at 8 years was 1.6 (1.8) in the BLRc group and 0.8 (1.1) in the R&R group (adjusted difference = 0.8; 95% CI = 0.0 to 1.5, P = 0.049). There were no statistically significant differences in means between the BLRc and R&R groups for near exotropia control, distance or near PACT magnitude, and near stereoacuity at the 8-year visit (Table 3).

Exploratory Outcomes – IXT-related Quality of Life and Diplopia at 8 Years

There were no substantial differences between the BLRc and R&R treatment groups in the distribution of the mean Rasch-based HRQOL scores for the child IXTQ and each of the three parent IXTQ domains (Tables 4, S5, and S6). On the Diplopia Questionnaire, diplopia in any direction in the past week was reported in 8 of 46 participants (17%) from the BLRc group and in 4 of 41 participants (10%) from the R&R group. For those four R&R participants who reported diplopia, 2 reported diplopia in side gaze, 1 in the direction of the non-operated eye (in the field of action of the operated medial rectus muscle), 1 in both the right and left gaze. Mean Diplopia Questionnaire scores at 8 years also did not differ substantially between treatment groups (Tables 4 and S7).

Postoperative Nonsurgical Treatment

During 8 years of follow-up, postoperative nonsurgical treatment was prescribed in 26% (26 of 101) of participants in the BLRc group and in 44% (42 of 96) in the R&R group (Table S8). Patching (alone or with other treatments) was prescribed for 4 (4%) and 26 (27%) of

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those in the BLRc and R&R groups, respectively. This difference was primarily due to more patching for esotropia being prescribed in the R&R group early in the post-operative course rather than patching for recurrent or residual exotropia. Orthoptic exercises (alone or with other treatments) were prescribed for 10 (10%) and 10 (10%) of participants in the BLRc and R&R groups, respectively; (Table S8).

Discussion

The IXT1 randomized clinical trial was designed to compare suboptimal surgical outcomes after BLRc versus R&R procedures, followed by usual care, for children with basic-type IXT. We now report that the cumulative incidence of suboptimal surgical outcome by 8 years was not significantly different between groups (68% in BLRc vs. 53% R&R: difference = 15%; 95% CI −2% to 32%); however, the 95% CI of the estimated difference did not exclude a possible moderate benefit of R&R, but it did exclude a moderate benefit of BLRc. This result is consistent with our previous report[5] of this cohort after three years of follow-up, in which the cumulative incidence of suboptimal surgical outcome was not statistically different between the two groups (46% in BLRc vs. 37% in R&R; difference = 9%; 95% CI = −6% to 23%), and the 95% CI did not exclude a possible moderate benefit of R&R but did exclude a moderate benefit of BLRc. It is noteworthy that four of our secondary outcomes (reoperation by 8 years, and complete or near-complete resolution, suboptimal surgical outcome at 8 years, and IXT distance control score at 8 years) also suggested a statistically significant benefit of R&R over BLRc, consistent with the trend observed in the primary outcome.

We are unaware of any previous studies that compare long-term outcomes between BLRc and R&R procedures for childhood IXT. Nevertheless, our data which suggest a benefit of R&R over BLRc for IXT are consistent with two previous RCTs reporting shorter-term outcomes. Kushner et al[6] found a benefit at 12 months of R&R versus BLRc for basic IXT (82% success for R&R vs. 52% for BLRc; N=17 and 19, respectively). Kushner hypothesized that the restrictive effect created by the medial rectus resection tethers the eye in place decreasing the tendency for an outward drift and recurrence. Kushner’s hypothesis is consistent with our finding that the primary reason for reoperation was residual or recurrent exodeviation, particularly when the initial surgery was BLRc, and that the reoperation rate over 8 years was significantly lower when the initial surgery was R&R. Similarly, Somer et al[7] reported 1-year success rates of 77% in 26 patients who underwent R&R and 48% in 21 patents who underwent BLRc. Conversely, Zhang et al[8] found no difference in 1-year success rates of 89% and 79% in patients who underwent R&R and BLRc, respectively (N = 58 in both groups), and the 3-year outcomes from the current RCT[5] did not indicate a statistically significant difference between R&R and BLRc in suboptimal surgical outcome by 3 years or reoperation by 3 years. Our report of 8-year surgical outcomes may be useful to patients, families, and clinicians by providing data regarding long-term alignment.

Another hypothesis consistent with the suggestion that BLRc results in worse long-term postoperative outcomes is that the dose tables used for the present study were insufficient for BLRc. It is noteworthy that while the original IXT1 protocol was in development, Lee and

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coauthors reported a case series that suggested better results with augmented bilateral lateral rectus muscle recessions.[18] It is possible that our study results may have differed from the current results had augmented surgery tables been used.

Although some might consider the rates of suboptimal surgical outcomes high, we suggest that our *a priori* definition of suboptimal surgical outcome was fairly liberal and our definition of complete or near-complete resolution was fairly strict. The severity of childhood intermittent exotropia is often judged by the parent and the provider as the level of control. Recent IXT treatment trials have used control as the primary outcome measure.[19,20] In the current RCT, if we consider an outcome measure that reflects control, it is noteworthy that at the final 8-year visit, 63% of the BLRc group and 72% of the R&R group did not have a spontaneous tropia during the examination or an average control score of 3 or higher at distance or near. These data suggest that the overall impact of strabismus surgery for childhood IXT, followed by usual care, appears to be more favorable than when judged using the study's primary outcome measure.

Our study has some limitations. First, we obtained 8-year outcome data in about half of our randomized cohort, and therefore we cannot rule out potential selection bias in our analysis. However, we found no appreciable differences in baseline characteristics between those who completed follow-up and those who did not. Second, reoperation was at investigator discretion after suboptimal surgical outcome for the first 3 years and at any time between 4 and 8 years. It is possible that the decision by the parent, child, and treating provider to reoperate might have been biased by the type of initial surgery.

In summary, we found that the cumulative incidence of a suboptimal surgical outcome by 8 years was not significantly different between BLRc and R&R, followed by usual care, for childhood basic-type IXT. Nevertheless, the 95% CI of the estimated difference did not exclude a possible moderate benefit of R&R whereas it did exclude a moderate benefit of BLRc. Taking this finding together with important secondary outcomes (including complete or near-complete resolution at 8 years and reoperation rate by 8 years) suggests that R&R may result in better long-term outcomes than BLRc using the surgical doses chosen for the present study. Overall, the results of surgery followed by usual care were somewhat disappointing, and therefore we need additional studies of alternative surgical and non-surgical treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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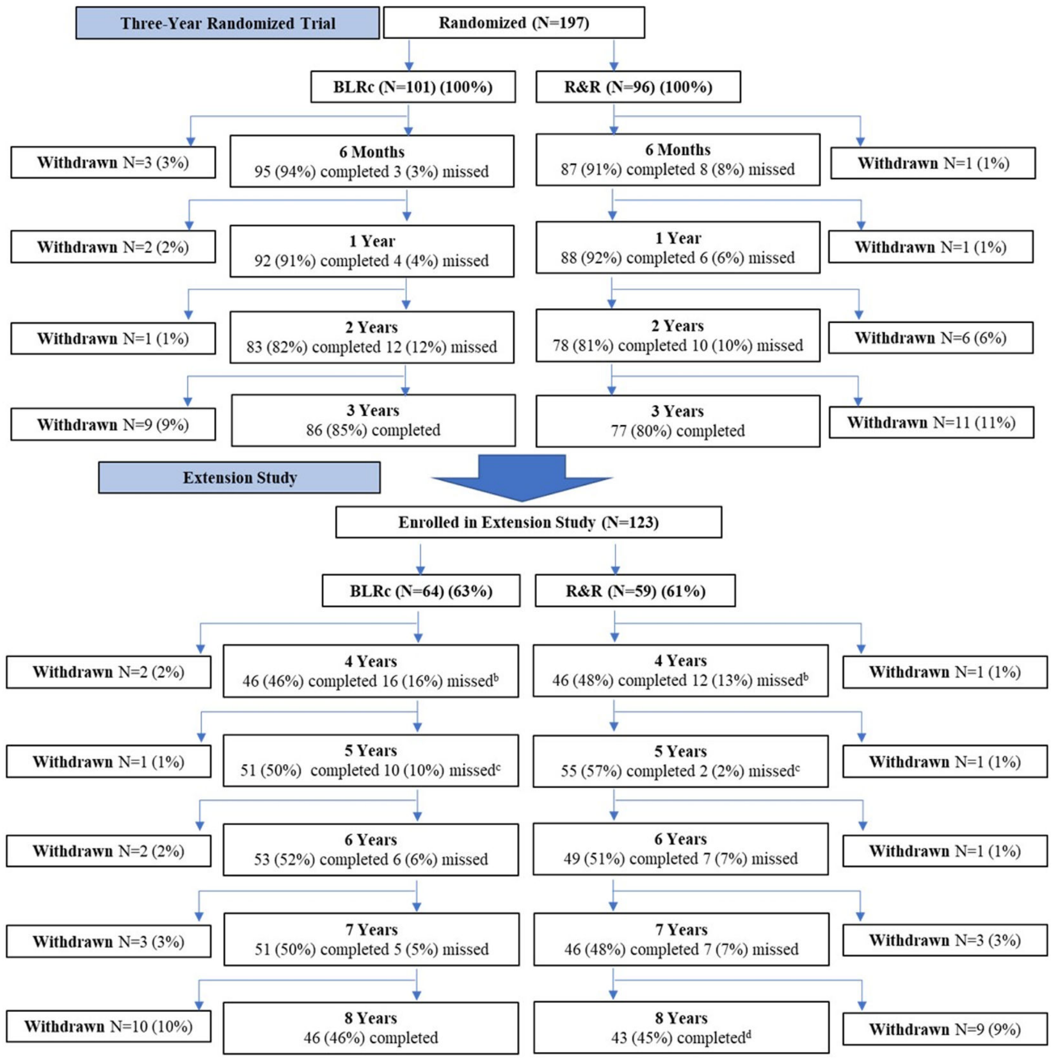

Figure 1. Flow of Participants through Study.

BLRc = bilateral lateral rectus muscle recession; R&R = unilateral lateral rectus recession combined with a medial rectus resection in same eye.

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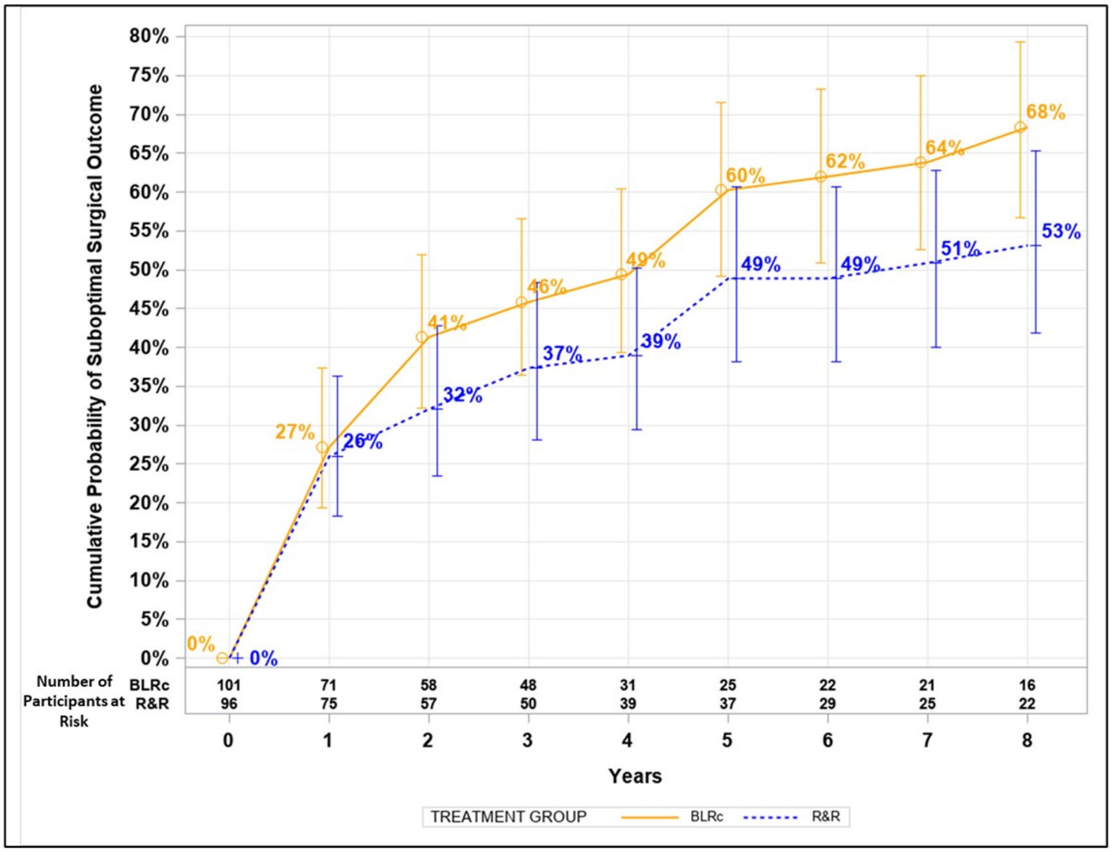

Figure 2. Suboptimal Surgical Outcome By 8 Years.

Cumulative probability (and 95% confidence interval) of suboptimal surgical outcome over 8 years from Kaplan-Meier analysis. BLRc = bilateral lateral rectus muscle recession; R&R = unilateral lateral rectus muscle recession combined with a medial rectus muscle resection in same eye

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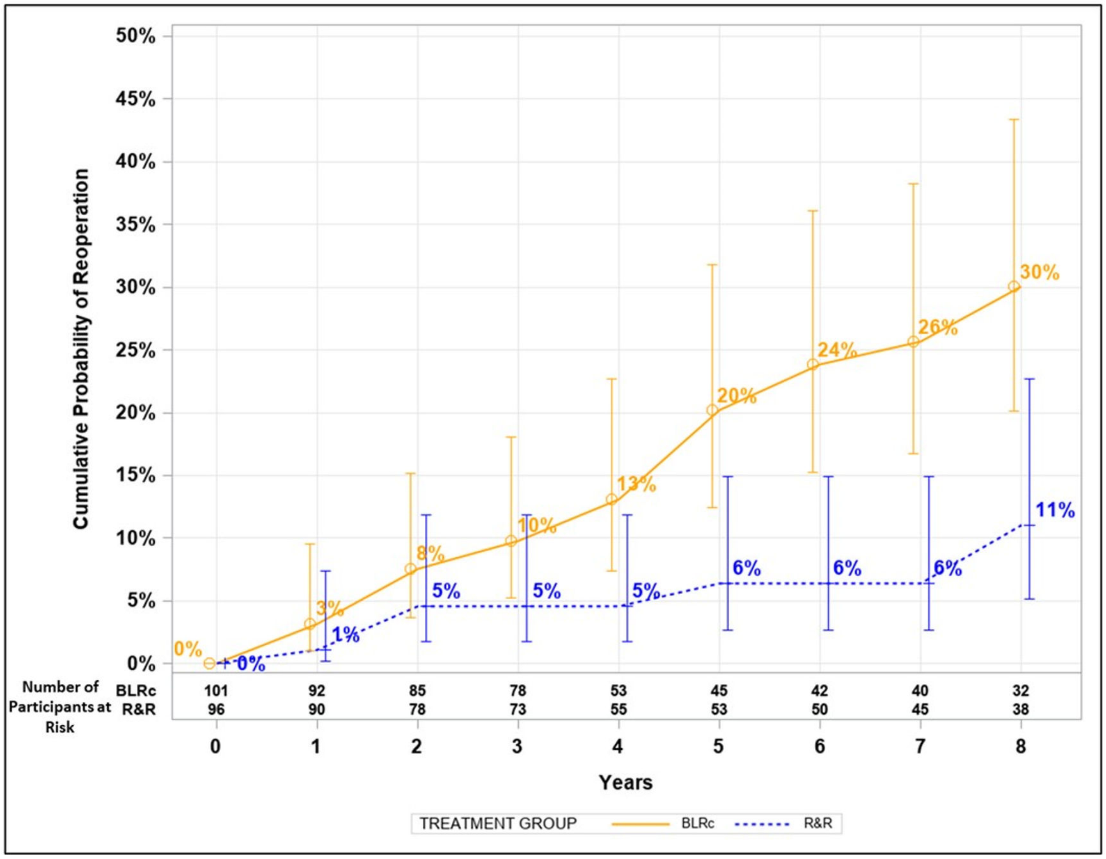

Figure 3: Reoperation by 8 Years.

Cumulative probability (and 95% confidence interval) of reoperation over 8 years from Kaplan-Meier analysis. BLRc = bilateral lateral rectus muscle recession; R&R = unilateral lateral rectus recession combined with a medial rectus resection in same eye. Among the reoperations occurred during the 8-year follow-up, in the BLRc and R&R groups, respectively, 90% (18 of 20) and 57% (4 of 7) were to correct residual or recurrent exotropia, 5% (1 of 20) and 43% (3 of 7) were to correct consecutive esotropia, and 5% (1 of 20) and 0% (0 of 7) were to correct inferior oblique over-action.

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Table 2.

Suboptimal Surgical Outcome at Follow-up Visits

	Randomized Trial Period						Extension Study Period										Total	
	0 to 1 Year		>1 Year to 2 Years		>2 Years to 3 Years		>3 Years to 4 Years		>4 Years to 5 Years		>5 Years to 6 Years		>6 Years to 7 Years		>7 Years to 8 Years			
	BLRc	R&R	BLRc	R&R	BLRc	R&R	BLRc	R&R	BLRc	R&R	BLRc	R&R	BLRc	R&R	BLRc	R&R	BLRc	R&R
N at risk	101	96	71	75	58	57	48	50	31	39	25	37	22	29	21	25	N/A	N/A
N with suboptimal surgical outcome	26	24	13	5	4	4	2	1	6	6	1	.	1	1	2	1	55	42
XT[a]	17	12	9	5	3	4	1	.	1	5	.	.	1	1	2	.	34	27
Constant ET[b]	1	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2
Stereo loss[c]	4	4	4	.	1	.	.	1	2	1	1	.	.	.	.	1	12	7
Stereo loss and XT	1	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	2	.
Stereo loss and constant ET	2	5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	5
Reoperated without meeting suboptimal surgical outcome	1	1	.	.	.	.	.	.	3	.	.	.	.	.	.	.	4	1
Cumulative probability of meeting suboptimal surgical outcome	27%	26%	41%	32%	46%	37%	49%	39%	60%	49%	62%	49%	64%	51%	68%	53%	N/A	N/A

Abbreviations: BLRc = Bilateral lateral rectus muscle recession, R&R = Unilateral lateral rectus muscle recess-medial rectus muscle resection.

[a] XT = exotropia ≥10Δ by SPCT at distance or near.

[b] Constant ET = constant esotropia ≥6Δ by SPCT at distance or near.

[c] Stereo loss = decrease in Preschool Randot near stereoacuity ≥0.6 log arcsec from enrollment, or to nil.

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Table 3.

Exotropia Control, PACT Magnitude and Near Stereo Outcomes at 8 Years

	BLRc (N = 46)		R&R (N = 43)		Treatment-Group Difference (BLRc – R&R)[a]		
	Mean (SD)		Mean (SD)		Difference	95% Confidence Interval	P
Control at Distance (0 to 5)	1.6	(1.8)	0.8	(1.1)	0.8	(0.0 to 1.5)	0.049
Control at Near (0 to 5)	1.1	(1.5)	0.6	(1.1)	0.5	(−0.2 to 1.1)	0.21
PACT at Distance (Δ)	11.6	(8.7)	9.3	(11.5)	2.3	(−2.6 to 7.1)	0.41
PACT at Near (Δ)	12.2	(10.5)	8.5	(13.1)	3.6	(−2.1 to 9.3)	0.25
Near Stereoacuity (logArcSec)[b]	2.0	(0.5)	1.9	(0.4)	0.1	(−0.1 to 0.3)	0.44
	N	(%)	N	(%)	Difference	95% Confidence Interval	P
Participants with spontaneous exotropia during the examination or average control score of 3 or higher at distance or near	17	(37%)	12	(28%)	9%	(−13% to 32%)	0.53
Participants with decrease in near stereoacuity ≥0.6 log arcsec from baseline [b]	7	(15%)	4	(9%)	6%	(−10% to 22%)	0.53

Abbreviations: BLRc = Bilateral lateral rectus muscle recession, PACT = Prism and alternate cover test, R&R = Unilateral lateral rectus muscle recess-medial rectus muscle resection in same eye SD = standard deviation.

[a]The confidence intervals and P values were adjusted using the adaptive false discovery rate (FDR) approach to account for multiplicity, with the overall FDR controlled at the 5% probability level. The analyses of control at distance, control at near, PACT at distance, PACT at near, and near stereoacuity were adjusted for corresponding measure at baseline.

[b]The near stereoacuity at 8 years was not available for 1 participant in the R&R group.

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Table 4.

Child Intermittent Exotropia Questionnaire (IXTQ), Parent IXTQ, and Diplopia Questionnaire Scores at 8 Years

	BLRc			R&R			Treatment-Group Difference (BLRc – R&R)		
	N	**Median**	**Interquartile Range**	**N**	**Median**	**Interquartile Range**	**Hodges-Lehmann Estimator[a]**	**95% Confidence Interval**	**P[b]**
IXTQ Domain Scores									
Child	46	86	(77 to 95)	41	91	(77 to 100)	0.0	(−9.1 to 4.6)	0.54
Parent Psychosocial Domain	42	97	(86 to 100)	40	98	(81 to 100)	0.0	(0.0 to 3.1)	0.86
Parent Function Domain	42	88	(78 to 94)	40	89	(78 to 97)	0.0	(−5.6 to 2.8)	0.67
Parent Surgery Domain	42	92	(69 to 100)	40	100	(83 to 100)	0.0	(−8.4 to 0.0)	0.45
Diplopia Questionnaire Scores	46	0	(0 to 0)	41	0	(0 to 0)	0.0	(0.0 to 0.0)	0.26

Abbreviations: BLRc = Bilateral lateral rectus muscle recession, R&R = Unilateral recess-resect, PACT = Prism and alternate cover test, IXTQ: Intermittent Exotropia Questionnaire.

[a]The Hodges-Lehmann estimator is the median of all paired differences.

[b]Wilcoxon Rank-Sum Test.

IXT2 – A Randomized Trial Comparing Part- Time Patching with Observation for Children 3 to 10 Years of Age with Intermittent Exotropia.

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A Randomized Trial Comparing Part-time Patching with Observation for Children 3–10 Years Old with Intermittent Exotropia

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Abstract

Objective—To determine the effectiveness of prescribed part-time patching for treatment of intermittent exotropia in children

Design—Multicenter, randomized clinical trial

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Participants—Three hundred fifty-eight children aged 3 to < 11 years old with previously untreated (except for refractive correction) intermittent exotropia (IXT) and near stereoacuity of 400 arcsec or better were enrolled. Intermittent exotropia met the following criteria: 1) constant or intermittent exotropia at distance and either intermittent exotropia or exophoria at near; 2) exodeviation (tropia or phoria) of at least 15 prism diopters (Δ) at distance or near by prism and alternate cover test (PACT); and 3) exodeviation of at least 10Δ at distance by PACT.

Methods—Participants were randomly assigned to either observation (no treatment for 6 months) or patching for 3 hours per day for 5 months, with a 1-month washout period of no patching before the 6-month primary outcome exam.

Main Outcome Measure—The primary outcome was deterioration at either the 3-month or the 6-month follow-up visit, defined as: 1) constant exotropia measuring at least 10Δ at distance and near by simultaneous prism and cover test, and/or 2) near stereoacuity decreased by at least 2 octaves from baseline, both assessed by a masked examiner and confirmed by a retest. Participants who were prescribed any non-randomized treatment without first meeting either deterioration criteria were also counted as having deteriorated.

Results—Of the 324 (91%) participants completing the 6-month primary outcome exam, deterioration occurred in 10 (6.1%) of the 165 participants in the observation group (3 of these 10 started treatment without meeting deterioration criteria) and in 1 (0.6%) of the 159 participants in the part-time patching group (difference = 5.4%, lower limit of one-sided exact 95% confidence interval = 2.0%; p value from one-sided hypothesis test = 0.004).

Conclusion—Deterioration of previously untreated childhood IXT over a 6-month period is uncommon with or without patching treatment. Although there is a slightly lower deterioration rate with patching, both management approaches are reasonable for treating 3 to 10 year olds with IXT.

Intermittent exotropia (IXT) is the most common form of childhood exotropia[1, 2] and the most prevalent form of strabismus in some populations.[3–5] IXT is characterized by periods of normal binocular alignment and sensory fusion some of the time and a manifest exotropia present at other times. Both surgical and non-surgical management options are commonly prescribed, but there is controversy regarding both the optimal timing and method of treatment. The rationale for non-surgical interventions is that they improve the ability to control the IXT and preserve stereoacuity, thereby potentially improving visual function and allaying social concerns. In some patients, it is possible that non-surgical treatments may also delay or eliminate the need for surgical intervention. Patching either the preferred eye or alternate patching is one of several prescribed non-surgical treatments for children affected by IXT.[6–9] Often prescribed as a method for delaying surgery,[10] the reported possible benefits[11–19] of patching include elimination of suppression, decreasing the frequency or magnitude of the deviation, and/or changing the character of the deviation (e.g., from constant exotropia to IXT or IXT to exophoria).

Although patching therapy for IXT is commonly prescribed, existing data on treatment effectiveness are limited. Published studies have varied in terms of patching dosage, duration, and outcome measures, and have reported varying success rates.[11–19] Furthermore, studies have been primarily retrospective with small sample sizes and conducted without

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comparison groups. As a result, there is no convincing evidence supporting the effectiveness of patching treatment for IXT. The objective of this randomized trial was to determine the effectiveness of prescribed part-time patching for reducing the risk of deterioration of IXT among 3 to <11-year-old children over a 6-month period.

Methods

The study was supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health, and was conducted according to the tenets of the Declaration of Helsinki, by the Pediatric Eye Disease Investigator Group (PEDIG) at 60 academic- and community-based clinical sites. The protocol and Health Insurance Portability and Accountability Act (HIPAA)–compliant informed consent forms were approved by institutional review boards, and a parent or guardian of each study participant gave written informed consent. An independent data and safety monitoring committee provided study oversight. The study is listed on www.clinicaltrials.gov (NCT01032330, accessed 12/3/13). The full study protocol is available on the PEDIG website (www.pedig.net, accessed 12/3/13).

The study that is described herein is a 6-month randomized trial to evaluate the short-term effect of part-time patching treatment compared with observation of IXT. It is the completed first phase of an ongoing study that also aims to evaluate the natural history of IXT in the observation group. The protocol for the 6-month randomized trial portion of the study is summarized below.

Eligibility Criteria

The study included children aged 3 to <11 years with previously untreated IXT (other than refractive correction) and near stereoacuity of 400 arcsec or better on the Preschool Randot Stereotest (Stereo Optical Co., Chicago, IL). For study eligibility, the IXT had to meet the following three criteria: 1) intermittent or constant exotropia at distance, and either IXT or exophoria at near; 2) exodeviation (tropia or phoria) magnitude of 15 prism diopters (Δ) or greater at distance or near measured by the prism and alternate cover test (PACT); and 3) exodeviation of 10Δ or greater at distance measured by the PACT. In addition, the investigator and the child’s family had to be willing to observe the IXT untreated (except for refractive correction) for 3 years unless specific criteria for deterioration were met. Additional eligibility criteria are shown in Table 1.

Enrollment/Randomization

A child was considered for the study after undergoing a routine eye examination that identified intermittent exotropia that appeared to meet the eligibility criteria. After informed consent, data were entered on the PEDIG website and participants were randomly assigned (using a permuted block design stratified by site) with equal probability to either observation or to 3 hours of daily patching.

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Treatment

Participants randomized to the observation group received no treatment (other than refractive correction, if needed) for 6 months unless protocol-specified deterioration criteria (Table 2) were met at a masked exam occurring at least 3 months after randomization. Subsequent treatment was at investigator discretion if protocol-specified deterioration criteria were met, although participants remained in the study for follow-up.

Participants randomized to the patching group were prescribed patching for 3 hours per day for 5 months (in addition to refractive correction, if needed). The choice of whether to patch one eye or to alternately patch was at investigator discretion. Patching group participants were instructed not to patch on the day of the 3-month visit to reduce the chance that the masked exam would reflect the immediate effect of patching. Patching group participants were also instructed to resume patching after the 3-month visit unless specific deterioration criteria were met, in which case further treatment was at investigator discretion. Patching was to be discontinued 4 weeks before the 6-month primary outcome visit as it was felt this might eliminate any effect that persists only during the patching treatment phase. Study calendars were dispensed at the enrollment and 3-month visits with the instruction that parents should record the numbers of hours their child patched each day and the eye patched.

Although investigators were strongly encouraged not to prescribe non-study treatment (any treatment in the observation group or treatment other than patching in the patching group) before a participant met formal protocol-specified deterioration criteria, exceptions were permitted by protocol if the participant was reported to have debilitating diplopia, there was overwhelming social concern on the part of the child or parent, or the participant failed to meet stereoacuity age norms on the Preschool Randot Stereotest.[20]

Testing Procedures and Follow-up Visits

Follow-up consisted of an interim visit 3 months (± 2 weeks) after randomization and a primary outcome exam at 6 months (± 1 month) after randomization. Additional visits during the first 6 months of the study were at investigator discretion. After the 6-month primary outcome exam, follow-up continued every 6 months through 3 years with further patching in the patching group at investigator discretion; 3-year follow-up data will be reported at a later time.

At each follow-up visit, a study-certified examiner (pediatric ophthalmologist, pediatric optometrist, or certified orthoptist) masked to the participant’s treatment group measured stereoacuity, assessed exotropia control, and measured ocular alignment. Distance stereoacuity was assessed using the Distance Randot test[21, 22] at 3 meters; near stereoacuity was assessed using the Preschool Randot test, Titmus Fly, and Titmus Circles tests at 40 centimeters. Control of the exodeviation was measured at distance (6 meters) and at near (1/3 meters) using the Office Control Score,[23] which ranges from 0 (phoria, best control) to 5 (constant exotropia, worst control). Control levels 3 to 5 are assigned based on the proportion of time that a manifest exotropia is present during a 30-second observation period before any dissociation. If no exotropia is observed during this period, control levels 0 to 2

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are assigned based on the longest time it takes for fusion to be reestablished following three consecutive 10-second periods of dissociation. Following control testing, distance (6 meters) and near (1/3 meter) ocular alignment were assessed using the cover/uncover test, simultaneous prism and cover test (SPCT), and PACT. If the participant's condition appeared to meet one or more protocol-specified criteria for deterioration on the initial masked exam testing, the masked examiner retested after a 10-minute break to determine whether deterioration was indeed met.

In addition to the masked portion of the exam, distance visual acuity was measured by a certified examiner using a testing protocol based on age at enrollment - the ATS HOTV©[24] testing protocol for children < 7 years or the electronic ETDRS (Early Treatment Diabetic Retinopathy Study) (E-ETDRS©)[25, 26] protocol for children aged ≥7 years.

For participants in the patching group, compliance with patching treatment was assessed at each follow-up visit. Investigators judged compliance to be excellent (>75%), good (51% to 75%), fair (26% to 50%), or poor (≤ 25%) based on discussions with the parent and by reviewing study calendars on which parents recorded the numbers of hours the child patched each day.

Primary Outcome

The primary outcome measure for this study was whether the participant's condition had deteriorated within 6 months after randomization. Deterioration was defined as meeting one or both of the following criteria during a masked examination at either the 3-month or 6-month visit: 1) a constant exotropia (throughout the exam) of 10Δ or greater at distance *and* near by SPCT, confirmed by a retest, or 2) loss of near stereoacuity of 2 octaves (0.6 log arcsec) or more from the better of a test and retest of Preschool Randot stereoacuity at baseline (Table 2), confirmed by a retest. A "constant" tropia was defined as a manifest tropia that was present 100% of the time during the examination, determined by cover/uncover tests performed at least three different times during the exam (one before any dissociation). In addition, participants were classified as deteriorated for the primary analysis if they started using non-randomized treatment (i.e., any treatment in the observation group; any treatment other than patching in the patching group) without first meeting one of the two protocol-specified deterioration criteria.

Statistical Methods

The trial was designed to evaluate whether patching reduces the 6-month risk of deterioration compared with observation alone in children aged 3–<11 years old. The sample size of 336 was chosen for the long-term primary analysis at 3 years. For the 6-month treatment group comparison, this sample size provided 92% power with a one-sided type I error rate of 5% to detect a difference given expected risks of deterioration of 15% in the observation group vs. 5% in the patching group, estimates which were based on expert consensus. The efficacy threshold was $p<0.0485$ as defined by the O'Brien-Fleming test,[27] adjusting for the 0.0015 type I error spent on a single interim efficacy analysis conducted in March 2011.

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The primary analysis was a treatment group comparison of the proportion of participants with deterioration occurring within 6 months of randomization using a one-sided Barnard's test.[28] The treatment group difference in the proportion with deterioration and the lower limit of a one-sided 95% exact confidence interval were calculated. A two-sided exact 95% confidence interval was also calculated to provide an upper limit on the estimate of the potential magnitude of the difference. The primary analysis was limited to participants who completed the initial testing for all primary-outcome-related testing components of the 6-month masked exam (i.e., stereoacuity, cover/uncover, and SPCT testing) regardless of whether any required retests were completed. If participants did not complete a visit within the 6±1 month protocol-specified window, the primary analysis included the first visit completed 3.5 to <5 months after randomization (N=3) or >7 to 10 months after randomization (N=20). Two participants who appeared to meet deterioration criteria on initial testing but who did not complete the required retest were considered not to have deteriorated. The primary analysis included 10 participants who were found to be ineligible after randomization (including 6 who had prior treatment for IXT) and 4 participants for whom visual acuity eligibility was assessed using a non-study method. The primary analysis also included 15 participants who completed the 6-month visit but did not complete the 3-month visit; these participants were assumed not to have deteriorated by 3 months and had their outcome based solely on data from the 6-month visit. Two data analysts independently performed the primary analysis. An alternative analysis used baseline data to impute 6-month data by multiple imputation with the logistic regression method[29] for the 34 participants who missed the 6-month masked exam; baseline data used for imputation consisted of age, presence of constant exotropia at distance, and SPCT magnitude at distance, all of which were associated with 6-month deterioration.

An additional analysis was conducted using a post-hoc alternative definition of deterioration which counted deterioration only if stereoacuity had worsened by at least 2 octaves by 6 months, regardless of whether the participant was judged to have a constant exotropia or had started non-protocol treatment in absence of meeting study-specified deterioration criteria.

We also evaluated 6-month secondary outcomes of near stereoacuity, exotropia control at distance and near, and magnitude of the deviation at distance and near measured by PACT. Outcomes from the 6-month visit were used unless the patient's IXT had deteriorated prior to 6 months, in which case the outcomes were obtained from the visit at which deterioration was first observed. Continuous outcomes were compared between treatment groups using analysis of covariance models adjusting for the baseline level of the outcome. Stereoacuity was evaluated as a continuous outcome by converting seconds of arc scores to log arcsec values as follows: 40 (1.60), 60 (1.78), 100 (2.00), 200 (2.30), 400 (2.60), 800 (2.90); participants with no detectable (nil) stereoacuity were assigned a value of 1600 (3.20). Two sets of binary variables assessed the proportion of patients who improved at least a specified amount and the proportion of patients who worsened at least a specified amount. Improvement in stereoacuity was defined as an improvement of ≥2 octaves (0.6 log arcsec) from baseline. For distance and near control, improvement was defined as a decrease of ≥3 points from the respective baseline value. Improvement in PACT at distance and near were defined as a decrease of ≥8Δ and ≥13Δ, respectively, because these amounts exceed the repeatability coefficients of 7.2Δ and 12.8Δ for PACT angles larger than 20Δ at distance and

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near.[30] The same cutoffs for change that represent improvement were also used to determine the proportion of patients who worsened on each outcome. Binary outcomes were compared between treatment groups using exact logistic regression models adjusting for the baseline level of the outcome (two-sided p values are reported). Each binary outcome was assessed in only those participants whose baseline level allowed for potential change (improvement or worsening) of the specified amount.

All analyses followed the intention-to-treat principle (i.e., the treatment group data were based on the randomized treatment assignment regardless of whether the treatment protocol was followed). Analyses were conducted using SAS version 9.3 (SAS Institute Inc. Cary, NC).

Results

Baseline Characteristics

Between January 2010 and September 2012, 358 children were enrolled at 60 clinical sites with 183 participants assigned to the observation group and 175 assigned to the patching group (Figure 1). The average age was 6.0 (±2.0) years, 213 (60%) were female, and 221 (62%) were white. IXT was classified as basic type (i.e., distance and near exodeviations within 10Δ by PACT) in 246 (69%) participants, pseudo divergence excess type in 78 (22%), true divergence excess type in 17 (5%), high AC/A (accommodative convergence to accommodation) ratio type in 11 (3%), and convergence insufficiency type in 5 (1%) (see protocol at www.pedig.net for details of IXT classification). Baseline characteristics appeared similar in both treatment groups (Tables 3 and 4).

Visit Completion

The 3-month visit was completed by 162 (89%) of the 183 participants in the observation group and by 158 (90%) of the 175 participants in the patching group. The 6-month primary outcome visit was completed by 165 (90%) participants in the observation group, (151 [92%] of whom completed the visit within the protocol-specified time window of 6 months ±1 month), and by 159 (91%) participants in the patching group, (150 [94%] of whom completed the visit within the protocol-specified time window of 6 months ±1 month). A masked examiner assessed the primary outcome in all but 6 cases. Compared with the 324 participants who completed the 6-month masked exam, the 34 participants who did not complete the 6-month masked exam (18 in observation group and 16 in patching group) had larger SPCT angles (18.1 vs. 13.5) and were more likely to be non-white (50% vs. 37%), but appeared similar on baseline factors such as age, near stereoacuity, PACT, and exotropia control. The reasons for not completing the 6-month primary outcome were similar for both treatment groups (Figure 1).

Treatment Compliance

At the 3-month visit, compliance with patching in the patching group was judged to be excellent in 116 (73%) participants, good in 29 (18%), fair in 8 (5%), poor in 4 (3%), 1 (1%) participant did not complete any patching, and patching compliance was unknown in 2 (1%). At the 6-month primary outcome visit, compliance with patching between 3 to 5 months after randomization was judged to be excellent in 112 (70%) participants, good in 29 (18%), fair in 8 (5%), poor in 5 (3%), 5 (3%) participants completed no patching during this period, and patching compliance was unknown in 1 (1%).

In the patching group, 19 (12%) participants stopped patching within 1 week of the 6-month visit, 4 (3%) stopped 1 to 3 weeks before, 100 (63%) stopped 3 to 5 weeks before (i.e., within 1 week of the 4-week target date as stipulated in the protocol), 11 (7%) stopped 5 to 7 weeks before, 23 (14%) stopped more than 7 weeks before, and 1 (1%) participant had never patched.

Four participants received treatment that deviated from the study protocol. One participant randomized to patching was not prescribed patching at enrollment because of miscommunication among clinic staff; this was detected at the 3-month visit and the participant started patching thereafter. In the observation group, 3 participants were started on treatment without meeting the formal criteria for deterioration; these were considered as deteriorations for analysis. In two cases, patching was started at the 3-month visit; in one case it was because of parents' social concerns and in the other case because of parents' concerns about their child's worsening exotropia control. In the other case, the clinical site mistakenly did not identify the child as a study participant at an office visit 5 months after randomization and the investigator prescribed treatment.

In the patching group, in the 6 months following randomization, investigators prescribed unilateral patching for 43 (25%) participants, alternate patching for 108 (62%), and both unilateral and alternate eye patching at different times for 8 (5%); the eye(s) patched was unknown in 16 (9%).

Primary Outcome by 6 Months

By the 6-month primary outcome exam, deterioration occurred in 10 (6.1%) of the 165 participants in the observation group and in 1 (0.6%) of the 159 participants in the patching group (difference = 5.4%; lower limit of one-sided exact 95% confidence interval (CI) = 2.0%, p value from one-sided hypothesis test = 0.004; two-sided exact 95% confidence interval = (1.6% to 10.3%) (Table 5). Of the 10 cases of deterioration in the observation group, 6 had stereoacuity worsen by at least 2 octaves, 1 was judged to have constant exotropia of at least 10Δ by SPCT at distance and near, and 3 did not meet either formal deterioration criterion but were considered deteriorations for the primary analysis because non-randomized treatment was started. The participant who met the constant exotropia deterioration criterion had a tropia of 30Δ at distance and 25Δ at near by SPCT, but also had 40 arcsec of near stereoacuity; therefore, it is unlikely the exotropia was truly constant (the masked examiner did not perform the protocol-specified cover/uncover test during stereoacuity testing to determine whether a tropia was present during stereoacuity testing—see Table 2). An additional observation group participant showed a 2-octave worsening in near stereoacuity on initial testing at the 6-month visit but was not retested to confirm the worsening; therefore, this participant's IXT was considered not to have deteriorated. The single instance of deterioration in the patching group was due to a participant's near stereoacuity worsening by at least 2 octaves. Additional clinical data for participants who experienced deterioration can be found in Table 6 (available at http://aaojournal.org). An

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analysis using multiple imputation with baseline data to impute the 6-month outcome for the 34 participants who did not complete the 6-month masked exam yielded similar results to the primary analysis (data not shown).

A secondary deterioration outcome based only on near stereoacuity worsening ≥2 octaves occurred in 6 (3.6%) of the 165 participants in the observation group and in 1 (0.6%) of the 159 participants in the patching group (difference = 3.0%, lower limit of one-sided exact 95% CI = 0.2%, p value from one-sided hypothesis test = 0.04).

Secondary Outcomes at 6 Months

Six months after randomization, the mean near stereoacuity was 1.84 arcsec (69 arcsec) in the observation group and 1.84 log arcsec (69 arc sec) in the patching group (p = 0.38) (Table 7, available at http://aaojournal.org). Among the 58 participants with baseline stereoacuity of 200 arcsec (2.3 log arcsec) or worse (who therefore could show improvement), a ≥2 octave improvement was found in 32% and 31% of the observation and patching groups, respectively (p = 0.32).

The mean distance control score at 6 months was 2.3 points in the observation group compared with 2.0 points in the patching group (p = 0.094) (Table 7, available at http://aaojournal.org). Among the 126 participants whose distance control was 3 points or worse at baseline, a ≥3 point improvement was observed in 10% of the observation group compared with 14% of the patching group (p = 0.81). At 6 months, the mean near control score was 1.2 and 0.9 points in the observation and patching groups, respectively (p = 0.013). In the 35 participants whose near control score was 3 points or worse at baseline, an improvement of ≥3 points was observed in 0% and 22% of the observation and patching groups, respectively (p = 0.20).

At 6 months, the mean magnitude of exotropia at distance by PACT was 23.8Δ in the observation group compared with 22.2Δ in the patching group (p = 0.012) (Table 7, available at http://aaojournal.org). A decrease of ≥ 8Δ in the distance magnitude was found in 9% of the observation group vs. 14% of the patching group (p = 0.17). The mean magnitude at near was 17.6Δ and 15.4Δ in the observation and patching groups respectively (p = 0.11). Among the 218 participants whose near magnitude measured at least 13Δ at baseline, a decrease of 13Δ or more was observed in 5% of the observation group and 10% of the patching group (p = 0.20).

The proportion of patients in each treatment group who worsened for each of the secondary outcomes is shown in Table 7 (available at http://aaojournal.org).

Discussion

We evaluated the effectiveness of prescribing 3 hours of daily patching compared with observation alone for reducing the risk of deterioration of IXT in previously untreated 3 to <11-year-old children. The rate of deterioration at 6 months post-randomization was low in both groups; only 0.6% in the patching group and 6.1% in the observation group deteriorated.

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We are not aware of any prospective randomized clinical trial that has compared prescribed part-time patching to observation in previously untreated children with IXT. The effects of part-time patching treatment for IXT have been reported in several studies that were either retrospective, had small sample sizes, or were conducted without a non-treated comparison group.[12–15, 17–19] These past non-randomized case series of varying amounts of part-time and full-time[11, 16] patching have generally reported treatment effectiveness in terms of improvement, defining “success” based on elimination of suppression,[11, 12] increased fusional vergence amplitudes,[11–13, 15] decreased magnitude of deviation,[12–19] or change in character of the exodeviation (i.e., constant XT to IXT or exophoria).[11–16, 18]

To evaluate the effectiveness of part-time patching in reducing the likelihood of deterioration of IXT, we defined our primary outcome measure of deterioration as the loss of motor control (IXT changing to a constant exotropia) or worsening of sensory fusion (decrease in stereoacuity). These criteria are consistent with common clinical teaching that worsening of motor control and/or stereoacuity is an indication to perform surgery.[10, 31] Given that we planned to enroll more than 300 children with previously untreated IXT with variable ages of onset, lengths of duration, angles of magnitude, and ability to control their IXTs, we predicted that a proportion of children would have their IXT deteriorate over the course of our study. Because we designed our study to also evaluate the natural history of untreated IXT, we chose strict criteria that would be widely accepted as reflecting true deterioration and also would allow investigators to prescribe non-randomized treatment in those cases: 1) a constant exotropia of $\geq 10\Delta$ at distance *and* near (motor criterion) or 2) a decrease in near stereoacuity of 2 or more octaves (sensory criterion). Nevertheless, during analysis, we discovered problems when allowing one criterion without another to determine failure. For example, documenting “constancy” of exotropia is fraught with potential pitfalls because patients with IXT often vary from tropia to phoria, and vice versa, over the course of a day and even within several minutes during an exam.[32] None of the 11 children in our study who were classified as “deteriorated” manifested deterioration on both motor and sensory criteria. As discussed earlier, the one child who was classified as deteriorated based on constant exotropia alone may not have truly deteriorated given the finding of excellent stereoacuity at near.

Four participants counted as deteriorations in the primary analysis either did not meet formal deterioration criteria (3) or were questionable (1). Of these, 2 participants were prescribed non-protocol treatment in the absence of constant exotropia or loss of stereoacuity and were counted as deteriorated in the primary analysis, consistent with our analysis plan, as was a third participant who was started on treatment without completing protocol testing. Because these 3 children were in the observation group, classifying them as deteriorated biased the primary outcome toward observing a benefit of patching. Conversely, considering them not deteriorated might have biased against finding an effect of patching if these participants would have eventually deteriorated had they not started non-randomized treatment. These cases reflected clinician and parental concern about possible worsening of the IXT, concerns which may have been influenced by knowledge of the treatment group and which are often key factors in the decision to proceed with IXT surgery.[33] In the fourth case, also in the

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observation group, a participant's excellent stereoacuity did not support the diagnosis of constant exotropia.

In an attempt to mitigate the impact of bias and misclassification, a secondary analysis was performed limiting the definition of deterioration solely to a worsening of ≥2 octaves of near stereoacuity, which occurred in 7 of the 10 deterioration cases, 6 of which were in the observation group. Assessing the study result only on the basis of near stereoacuity, 6 (3.6%) in the observation group and 1 (0.6%) in the patching group deteriorated, for a difference of 3.0%, provides support for the small treatment effect of patching found in our primary analysis.

Defining deterioration of IXT based on a decrease in near stereoacuity is also not without problems. Holmes et al[34] reported that 6 (7%) of 95 children who were observed without treatment showed a 2-octave reduction in a single measure of near stereoacuity, with 4 of the children demonstrating a return to baseline stereoacuity levels at a later visit, emphasizing the need for confirmatory retesting[34] at the same or a subsequent visit. Because our current study required a stereoacuity retest the same day, it is possible that some of those classified as "deteriorated" may have tested poorly because they were not feeling well or were uncooperative that day or because of the inherent variability of IXT. Nevertheless, any overestimation of stereoacuity deterioration resulting from not requiring a retest on a subsequent day would be minimal given the small magnitude of stereoacuity deterioration in both treatment groups (3.6% and 0.6%). Furthermore, any small overestimation of deterioration in stereoacuity is unlikely to have affected the treatment group comparison, as deterioration in both groups is expected to be overestimated by the same amount given that the treatment groups did not differ with respect to change in stereoacuity.

In addition to our primary outcome of deterioration, we also conducted secondary analyses to evaluate near stereoacuity, exotropia control, and magnitude of the deviation at 6 months. Although substantial improvements in sensory and/or motor fusion after patching for IXT have been reported in small case series and non-randomized studies,[11–16, 18] these did not occur in the present study. We found no difference between our patching and observation groups at 6 months in mean near stereoacuity, IXT control at distance, or magnitude of the exodeviation at near, and found marginally better mean near control and mean magnitude of the exodeviation at distance in the patching group. While an improvement in near control of ≥3 points on the 5-point scale or a decrease in the exodeviation magnitude by at least 8Δ at distance would likely be meaningful to most clinicians, we did not find a statistical difference between the 2 treatment groups using these criteria, although our study had very few patients with poor near control at baseline. Analyzing the proportion of patients who worsened over time we see that not only did very few participants meet our strict definition of deterioration, few participants in either group demonstrated substantive worsening in terms of control, PACT, or stereoacuity at near.

Our study is not without limitations. The proportion of patients with data available for analysis was 90% and 91% in the observation and patching groups, respectively, was lower than anticipated. Participants lost to follow-up could have an impact on the overall findings if they differed from those who completed the study, although our analysis found that both

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groups had similar baseline characteristics except for race/ethnicity. Additionally, protocol-approved exceptions for starting treatment in the absence of deterioration were used twice (in order to develop a protocol acceptable to our investigators, some exceptions to constancy of exotropia and loss of near stereoacuity were allowed for starting non-protocol treatment) and one participant was started on treatment without completing protocol testing, so it is unknown whether motor or stereoacuity deterioration criteria were met. As discussed earlier, classifying these cases as deteriorated in the primary analysis may have introduced bias, particularly given that the parents and investigators making these decisions were unmasked to treatment group. Also, one or more statistically significant findings might have occurred by chance (i.e. a false positive) given that we used multiple statistical tests. In addition, learning and/or age effects may have contributed to overestimating the proportion of patients with stereoacuity improvement, although we would expect that both treatment groups would be affected similarly. Finally, the one-time administration of the office-based control assessment used in this study has recently been reported to inadequately represent overall control.[35] New methods such as averaging the control scores from multiple assessments[35] may be needed to quantify control more rigorously in future studies.

Our results can be generalized only to children aged 3 to <11 years old who have previously untreated IXT, at least 400 arcsec of near stereoacuity, who share other similar clinical characteristics with our cohort, and are prescribed 3 hours of daily patching for 5 months followed by one month off treatment. First, we did not include IXT cases with very poor near stereoacuity. Second, it is possible that our investigators did not enroll the most severe cases of IXT, because the protocol required willingness to follow the child without treatment for 3 years unless specific deterioration criteria were met. Third, it is possible that patching for more than 3 hours daily or continuing patching treatment beyond 6 months might change the difference in deterioration rates between treatment groups. Finally, it is possible that the study results might have differed with an alternate study design such as one that required patching of the dominant eye only or that mandated corrective lenses for low amounts of hyperopia.

The present study possesses a number of strengths over prior case series and retrospective reviews. First, it is a randomized clinical trial comparing patching with observation in children with previously untreated IXT. Second, participants were evaluated using standardized measures by certified examiners who were masked to treatment assignment. Third, the study is comprised of a large, well-defined cohort that represents a wide spectrum of children with IXT.

Several advantages and disadvantages of part-time patching should be considered as clinicians and parents discuss treatment options. In addition to reducing the risk of deterioration of IXT by about 5%, part-time patching treatment is low cost, has low risk of harm, and can be administered by the child's caregiver. Conversely, completing what amounts to a total of 450 hours of patching treatment can pose difficulties for the child and caregiver. In addition to the psychosocial distress of wearing a patch,[36] the sensation of the patch on the face, skin irritation, and instability can also be problematic. The additional supervision and attention required to ensure that children comply with patching can be challenging for caregivers.[37] The overall burden of treatment may differ between families and is one factor to weigh against the potential benefits of treatment. From a public health perspective, the number of children who would need to be treated with our patching regimen in order to prevent a single deterioration would be 19 based on the 5.4% difference accounting for all instances of deterioration and 33 based on the 3.0% difference in the outcome due solely on a reduction in stereoacuity.

In conclusion, deterioration of previously untreated childhood IXT over a 6-month period is uncommon with or without patching treatment. Although there is a slightly lower deterioration rate with patching, both management approaches are reasonable for treating 3 to 10 year olds with IXT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1

Clinical Sites

Sites are listed in order by number of participants enrolled. Personnel are listed as (I) for Investigator, (C) for Coordinator, or (E) for Masked Examiner.

West Des Moines IA – Wolfe Eye Clinic (51)

Donny W. Suh, (I); Jody L. Jackson, (C); Jill J. Frohwein, (C); Autumn Parrino, (C); Lisa M. Fergus, (E)

Rockville MD – Stephen Glaser, M.D., P.C. (47)

Stephen R. Glaser, (I); Monica M. Pacheco, (I); Laura L. Graham, (C); Deandra B. Andrade, (C); Noga Senderowitsch, (C); Aliza C. Shabanowitz, (C); Nancy A. Morrison, (E)

Salt Lake City UT – Rocky Mountain Eye Care Associates (35)

David B. Petersen, (I); Tori S. Pickens, (C); J. Ryan McMurtrey, (E)

Montreal, Quebec, Canada – Centre Hospitalier Universitaire Sainte-Justine (28)

Rosanne Superstein, (I); Nicole X. Fallaha, (I); Caroline X. Belanger, (I); Maryse Thibeault, (C); Amandine L. Guinard, (E); Emma X. Chilliet, (E); Bouchra Lakhlif, (E); Charlotte Riguidel, (E)

Erie PA – Pediatric Ophthalmology of Erie (27)

Nicholas A. Sala, (I); Allyson M. Sala, (C); Rhonda M. Hodde, (C); Jeanine M. Romeo, (C); Veda L. Zeto, (E)

Nashville TN – Vanderbilt Eye Center (26)*

Sean P. Donahue, (I); Robert L. Estes, (I); David G. Morrison, (I); Lori Ann F. Kehler, (I); Lisa A. Fraine, (C); Jessica M. Kane, (C); Ronald J. Biernacki, (E); Kelsie J. Haskins, (E); Neva J. Fukuda, (E)

Rochester MN – Mayo Clinic (25)*

Jonathan M. Holmes, (I); Brian G. Mohney, (I); Tomohiko Yamada, (I); Rebecca A. Nielsen, (C); Sarah R. Hatt, (C); David A. Leske, (C); Lindsay D. Klaehn, (E); Laura Liebermann, (E)

*Members of the Pediatric Eye Disease Investigator Group (PEDIG) participating in the study are listed online in Appendix 1 (available at www.aaojournal.org).

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Houston TX – Baylor College of Medicine, Texas Children's Hospital – Department of Ophthalmology (24)

Evelyn A. Paysse, (I); Paul G. Steinkuller, (I); Kimberly G. Yen, (I); David K. Coats, (I); Mohamed A. Hussein, (I); Lingkun Kong, (C); Jane C. Edmond, (E)

Norfolk VA – Eastern Virginia Medical School (24)

Earl R. Crouch Jr., (I); Earl R. Crouch III, (I); Gaylord G. Ventura, (C)

Chicago Ridge IL – The Eye Specialists Center, L.L.C. (21)

Benjamin H. Ticho, (I); Megan Allen, (I); Alexander J. Khammar, (I); Deborah A. Clausius, (C); Sharon L. Giers, (C); Lindsay A. Horan, (E)

The Woodlands TX – Houston Eye Associates (19)

Aaron M. Miller, (I); Jorie L. Jackson, (C); Jay S. South, (E)

Winston-Salem NC – Wake Forest University (17)

Richard G. Weaver, (I); Eric W. Hein, (I); Cara P. Everhart, (C); Lori T. Cooke, (C); Angela Z. Moya, (E)

Birmingham AL – University of Alabama at Birmingham School of Optometry (15)

Wendy L. Marsh-Tootle, (I); Robert P. Rutstein, (I); Katherine K. Weise, (I); Marcela Frazier, (I); Kristine B. Hopkins, (I); Michelle B. Bowen, (C); Michael P. Hill, (C); Ross B. Roegner, (C); Sarah D. Lee, (E)

Durham NC – Duke University Eye Center (15)

Laura B. Enyedi, (I); David K. Wallace, (I); Tammy L. Yanovitch, (I); Sarah K. Jones, (C); Lois B. Duncan, (E); Namita X. Kashyap, (E)

Atlanta GA – The Emory Eye Center (14)

Scott R. Lambert, (I); Amy K. Hutchinson, (I); Phoebe D. Lenhart, (I); Judy L. Brower, (C); Marla J. Shainberg, (E); Natario L. Couser, (E)

Concord NH – Concord Eye Care P.C. (14)

Christie L. Morse, (I); Maynard B. Wheeler, (I); Melanie L. Christian, (C); Alannah O. Price, (C); Caroline C. Fang, (E); Virginia X. Karlsson, (E)

Lancaster PA – Family Eye Group (13)

David I. Silbert, (I); Noelle S. Matta, (C); Garry L. Leckemby, (E); Prucilla R. Shady, (E)

Fullerton CA – Southern California College of Optometry (13)

Susan A. Cotter, (I); Carmen N. Barnhardt, (I); Angela M. Chen, (I); Kristine Huang, (I); Paula A. Handford, (I); Reena A. Patel, (I); Raymond H. Chu, (I); Lisa M. Edwards, (I); Catherine L. Heyman, (I); Sue M. Parker, (C); Maedi M. Bartolacci, (C)

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Miami FL – Bascom Palmer Eye Institute (13)

Susanna M. Tamkins, (I); Craig A. McKeown, (I); Carolina Manchola-Orozco, (C); Courtney E. Ewert, (C); Priya X. Joshi, (C); Mariana Nunez, (C); Andriana X. Stas, (C); Kara M. Cavuoto, (E); Ta C. Chang, (E); Adam S. Perlman, (E);

Albuquerque NM – Children's Eye Center of New Mexico (13)

Todd A. Goldblum, (I); Kenneth P. Adams, (I): Angela Alfaro, (C)

Cranberry Township PA – Everett and Hurite Ophthalmic Association (11)

Darren L. Hoover, (I); Christine J. Deifel, (C); Jasbir K. Sayal, (C); Kari E. Soros, (C); Pamela A. Huston, (E);

Durham NC – North Carolina Eye, Ear, & Throat (11)

Joan T. Roberts, (I); Heather M. Klem, (C); Lynelle G. Perez, (C); Marguerite J. Sullivan, (E)

Gainesville FL – University of Florida Shands Hospital (11)

Nausheen Khuddus, (I); Tammy T. Price, (C); Kati M. Ostvig, (E)

Chicago IL – Ann & Robert H. Lurie Children's Hospital of Chicago (10)

Bahram Rahmani, (I); Hawke H. Yoon, (I); Yana Kiesau, (I); Aaliyah Hamidullah, (C); Kristyn M. Albert, (E); Heath W. Barto, (E); Marianne Mottier, (E); Vivian Tzanetakos, (E);

Lisle IL – Progressive Eye Care (9)

Patricia L. Davis, (I); Charita L. Smith, (C); Kathy A. Anderson, (E); Indre M. Rudaitis, (E);

Alberta Calgary, Canada – Alberta Children's Hospital (8)

William F. Astle, (I); Kenneth G. Romanchuk, (I); Emi N. Sanders, (C); Ania M. Hebert, (C); Christine M. Millar, (C); Heather J. Peddie, (C); Stacy Ruddell, (C); Heather N. Sandusky, (C); Trena L. Beer, (E); Zuzana X. Ecerova, (E); Charlene D. Gillis, (E); Catriona I. Kerr, (E); Shannon L. Steeves, (E)

New York NY – State University of New York, College of Optometry (8)

Marilyn Vricella, (I); Robert H. Duckman, (I); Sara Meeder, (C); Ida Chung, (E)

Minneapolis MN – University of Minnesota (7)[*]

C. Gail Summers, (I); Erick D. Bothun, (I); Inge De Becker, (I); Sara J. Downes, (I); Ann M. Holleschau, (C); Anna I. de Melo, (E); Katherine M. Hogue, (E); Kim S. Merrill, (E)

Chicago IL – Illinois College of Optometry (6)

Yi Pang, (I); Megan Allen, (I); Elyse Nylin, (C); Anesu H. Mvududu, (C); Christine L. Allison, (E); Brian W. Caden, (E)

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Halifax Nova Scotia, Canada IWK Health Centre (6)

G. Robert LaRoche, (I); Stephen C. Van Iderstine, (C); Leah A. Walsh, (C); Erik K. Hahn, (E)

Philadelphia PA – Salus University/Pennsylvania College of Optometry (5)

Mitchell M. Scheiman, (I); Karen E. Pollack, (C); Ruth Y. Shoge, (E); Lynn H. Trieu, (E)

Baltimore MD – Greater Baltimore Medical Center (4)

Mary Louise Z. Collins, (I); Allison A. Jenson, (I); Maureen A. Flanagan, (C); Kelsey A. Black, (E); Cheryl L. McCarus, (E); Saman Bhatti, (E)

Boston MA – Boston Medical Center (4)

Jean E. Ramsey, (I); Stephen P. Christiansen, (I); Elise N. Harb, (I); Vanessa C. Vazquez, (C); Kelly M. Castle, (E); Jennifer E. Lambert, (E)

Houston TX – University of Houston College of Optometry (4)

Ruth E. Manny, (I); Heather A. Anderson, (I); Karen D. Fern, (I); Catherine E. McDaniel, (I); Joan Do, (C); Kimberly Paz, (C); Gabynely G. Solis, (C)

Bronx NY – Montefiore Medical Center (4)

Ilana B. Friedman, (I); Louise V. Wolf, (C); Evelyn K. Koestenblatt, (C); Irina Katkovskaya, (E)

Spokane WA – Spokane Eye Clinic (4)

Jeffrey D. Colburn, (I); Eileen Dittman, (C); Marilyn M. Westerman, (E)

Charleston SC – Medical University of South Carolina, Storm Eye Institute (3)

Edward W. Cheeseman, (I); Mae M. Peterseim, (I); Carol U. Bradham, (C); Margaret E. Bozic, (C); Richard A. Saunders, (E); Ronald W. Teed, (E)

Columbus OH – The Ohio State University (3)

Marjean T. Kulp, (I); Freda D. Dallas, (C); Nancy E. Stevens, (C); Tamara S. Oechslin, (E); Andrew J. Toole, (E)

Portland OR – Pacific University of College of Optometry (3)

Richard London, (I); Jayne L. Silver, (C); James J. Kundart, (E)

Bloomington IN – Indiana University School of Optometry (3)

Don W. Lyon, (I); Tawna L. Roberts, (I); Kristy M. Dunlap, (C); Sara C. Long, (C); Vivian M. Wong, (E)

Rochester NY – University of Rochester Eye Institute (3)

Matthew D. Gearinger, (I); Elisabeth Carter, (C); Karen D. Skrine, (C)

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Sacramento CA – University of California Davis, Department of Ophthalmology (3)

Mary O'Hara, (I); Tania X. Hashmi, (C); Shaista Farooqui, (C); Nandini G. Gandhi, (E); Hai Tong, (E)

Columbia SC – University of South Carolina School of Medicine (3)

Edward W. Cheeseman, (I); Michelle M. Bass, (C); Robert B. North, (E)

Philadelphia PA - St. Christopher's Hospital for Children, Department of Ophthalmology (3)

Robert T. Spector, (I); Heena Patel, (C); JoAnn T. Bailey, (E)

Iowa City IA – University of Iowa Hospitals and Clinics (2)

Susannah Longmuir, (I); Wanda I. Ottar Pfeifer, (C); Richard J. Olson, (E); Megan K. Campbell, (E)

Cleveland OH – Rainbow Babies & Children's Hospital Department of Ophthalmology (2)

Faruk H. Orge, (I); Beth J. Colon, (C); Alicia M. Baird, (C); Nina X. Mar, (C); Sara E. Schoeck, (E); Florin Grigorian, (E)

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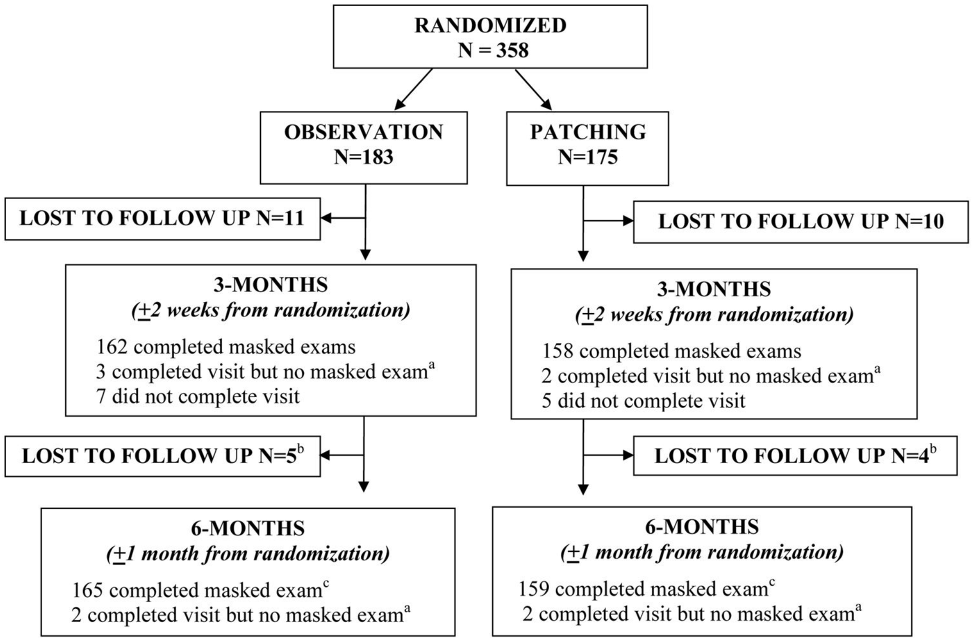

Reasons For Missing 6-Month Primary Outcome	Observation Group N=18	Patching Group N=16
Had visit but did not complete masked exam portion	2 (11%)	2 (13%)
Unable to locate patient	6 (33%)	3 (19%)
Difficulty contacting subject	7 (39%)	6 (38%)
Patient elected to withdraw for study-treatment related reason	1 (6%)	3 (19%)
Other	2 (11%)	2 (13%)

Figure 1. Flow of Participants through Study

[a]For the 3-month visit, 3 participants in the observation group and 2 participants in the patching group had the visit but did not complete some or all of the masked exam portion. For the 6-month visit, 2 participants in each treatment group had the visit but did not complete some or all of the masked exam portion.

[b]Includes 4 observation group participants and 2 patching group participants who are continuing in longer-term study follow-up but did not complete the 6-month visit and therefore are excluded from the primary analysis.

[c]Number of participants completing the initial masked exam testing at the 6-month visit (i.e. criteria for *inclusion* in the 6-month analysis), regardless of whether they met deterioration criteria at 3 months. Of these participants, those who met deterioration criteria at the 3-month visit were considered to be deteriorated by 6 months.

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Table 1

Eligibility Criteria

The following criteria must be met for enrollment into the study:

1 Age 3 to <11 years

2 Intermittent exotropia (IXT) - a manifest deviation meeting all of the following criteria:

- Intermittent exotropia at distance OR constant exotropia at distance and either intermittent exotropia or exophoria at near
- Exodeviation at least 15 prism diopters (Δ) at distance OR near measured by prism and alternate cover test (PACT)
- Exodeviation at least 10Δ at distance measured by PACT

3 No previous surgical or non-surgical treatment for IXT other than refractive correction (e.g., vergence therapy, patching, vision therapy/orthoptics, or deliberate over-minus with spectacles more than 0.50D)

4 No vision therapy/orthoptics for any reason within the last year

5 No previous amblyopia treatment other than refractive correction within 1 year

6 Investigator not planning to initiate amblyopia treatment

7 Near stereoacuity of 400 arcsec or better on the Preschool Randot Stereoacuity test

8 Visual acuity in the worse eye 0.3 logMAR or better (20/40 on ATS HOTV for patients 3 to < 7 years old or 70 letters on E-ETDRS© for patients ≥ 7 years old)

9 No hyperopia greater than +3.50 D spherical equivalent in either eye

10 No myopia greater than −6.00 D spherical equivalent in either eye

11 Patients must be wearing refractive correction (spectacles or contact lenses) for at least one week if refractive error (based on cycloplegic refraction performed within 6 months) meets any of the following:

- Myopia > −0.50 D spherical equivalent in either eye
- Anisometropia > 1.00 D spherical equivalent
- Astigmatism in either eye > 2.00 D if ≤ 5 years old and > 1.50 D if > 5 years old

Refractive correction must meet the following guidelines:

- Anisometropia spherical equivalent must be within 0.25 D of the full anisometropic difference correction
- Astigmatism cylinder must be within 0.25 D of full correction and axis must be within 5 degrees of full correction
- For hyperopia and myopia, the spherical component can be reduced by investigator discretion provided reduction is symmetrical and results in residual (i.e., uncorrected) spherical equivalent refractive error that does not exceed +3.50 D spherical equivalent hyperopia or −0.50 D spherical equivalent myopia.
- Deliberate over-minus using refractive correction with more than 0.50 D of over-minus will not be allowed. However, not prescribing the full cycloplegic hyperopic correction (i.e., prescribing reduced plus) is not considered the same as overmin using for this protocol and is therefore allowed

12 No atropine use within the last week

13 Gestational age > 34 weeks

14 Birth weight > 1500 grams

15 Investigator willing to observe the IXT untreated for 3 years unless specific deterioration criteria are met. Investigator also willing to forgo extraocular muscle surgery for the first 3 months in all cases, and from 3 months to 3 years unless specific deterioration criteria are met.

16 Patient and/or parent understands protocol, is willing to accept randomization to either observation or patching, and is willing to accept that surgical or other non-surgical treatment (other than patching in the patching group) of IXT will not be offered by the investigator unless specific deterioration criteria are met.

17 Parent has home phone (or access to phone) and is willing to be contacted by Jaeb Center staff

18 Relocation outside of area of an active PEDIG site within next 3 years not anticipated

19 No limitation of ocular rotations due to restrictive or paretic strabismus

20 No craniofacial malformations affecting the orbits

21 No prior strabismus surgery or botulinum injection, intraocular surgery, or refractive surgery

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22	No ocular disorders which would reduce visual acuity (except refractive error)
23	No known skin reactions to patch or bandage adhesives
24	No strabismus surgery planned
25	No significant neurological impairment such as cerebral palsy. Patients with mild speech delays or common reading and/or learning disabilities are not excluded.
26	Investigator not planning to change refractive correction at this time

IXT = intermittent exotropia; Δ = prism diopter; PACT = prism and alternate cover test; D = diopter; arcsec = seconds of arc; logMAR = logarithm of the minimum angle of resolution; E-ETDRS© = electronic ETDRS (Early Treatment Diabetic Retinopathy Study)

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Table 2

Definition of Deterioration by Six Months

Deterioration (Primary Outcome)

The participant's IXT was considered to have deteriorated if ANY of the following three criteria are met during masked examiner testing occurring at any protocol-specified or additional visit between 3 and 6 months from randomization:

1 Constant exotropia ≥10Δ at distance **AND** near (throughout exam) by SPCT, confirmed by a retest

- A "constant" tropia was defined as a manifest tropia that was present 100% of the time during the examination, determined by at least 3 cover/uncover tests (one before any dissociation).
- Because any amount of near stereoacuity may be inconsistent with a constant near tropia of 6Δ or larger, if the child appeared to have a constant tropia and near stereoacuity on the Preschool Randot Stereotest, the masked examiner was instructed to look over the child's Polaroid glasses while the child viewed the 800 arcsec stereogram while performing a cover/uncover test to determine if the child was tropic at the time he/she was reporting stereoacuity. If the child was not tropic at the time he/she was reporting stereoacuity, the near tropia was not considered to be constant.

2 Drop in near stereoacuity by Preschool Randot Stereotest of at least 2 octaves (at least 0.6 log arcsec) from *baseline* stereoacuity confirmed by a retest (see below)

Preschool Randot Near Stereoacuity	
Baseline stereoacuity, in arcsec	**Stereoacuity level needed at follow-up visit to meet deterioration criteria, in arcsec**
40″	200″ or worse
60″	400″ or worse
100″	400″ or worse
200″	800″ or worse
400″	Nil

3 Surgical or non-surgical treatment for IXT has been received (other than patching in the patching group) without first meeting either of the above deterioration criteria.

IXT = intermittent exotropia; SPCT = simultaneous prism and cover test; PACT = prism and alternate cover test; Δ = prism diopter; arcsec = seconds of arc

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Table 3

Baseline Demographic and Clinical Characteristics by Treatment Group

	Observation N=183		Patching N=175	
	N	**%**	**N**	**%**
Sex: Female	115	63	98	56
Race/ethnicity				
White	112	61	109	62
Black/African American	23	13	25	14
Hispanic or Latino	32	17	22	13
Other	14	8	13	7
Unknown/not reported	2	1	6	3
Age at randomization, years				
3 to <5	61	34	68	39
5 to <7	67	37	64	37
7 to <9	33	17	26	15
9 to <11	22	12	17	10
Mean (SD)	6.1 (2.0)		5.9 (2.0)	
Range	3.0 to 11.0		3.1 to 10.9	
Average visual acuity[a]				
20/12 or 20/16	21	11	22	13
20/20	65	36	70	41
20/25	73	40	45	26
20/32	17	9	28	16
20/40 or worse[b]	7	4	6	4
Mean (SD), logMAR	0.04 (0.09)		0.04 (0.10)	
Range, logMAR	−0.27 to 0.30		−0.15 to 0.50	
Interocular difference in visual acuity[a]				
0 lines	86	47	85	50
>0 to <1 line	45	25	37	22
1 line	42	23	43	25
>1 to <2 lines	4	2	5	3
≤ 2 lines[b]	6	3	1	1
Mean (SD), logMAR	0.05 (0.06)		0.04 (0.05)	
Range, logMAR	0.00 to 0.30		0.00 to 0.20	
Spectacle wear	42	23	38	22
Preschool Randot near stereoacuity, arcsec				
40″	75	41	69	39

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	Observation N=183		Patching N=175	
	N	%	N	%
60″	39	21	43	25
100″	43	23	25	14
200″	19	10	16	9
400″	7	4	22	13
Median	1.78		1.78	
Mean (SD) (log arcsec)	1.84 (0.27)		1.89 (0.34)	
Distance stereoacuity, arcsec[c]				
60″	64	35	77	44
100″	39	21	38	22
200″	30	16	23	13
400″	18	10	20	11
Nil	28	15	16	9
Median	2.00		2.00	
Mean (SD) (log arcsec)	2.22 (0.50)		2.12 (0.44)	
Exotropia type[d]				
Basic	127	69	119	68
Convergence insufficiency	5	3	0	0
High AC/A	4	2	7	4
Pseudo divergence excess	39	21	39	22
True divergence excess	7	4	10	6

[a]Four participants (2%) in the patching group have missing values because a non-PEDIG protocol was used for visual acuity testing.

[b]One participant in the patching group had 20/63 acuity and was ineligible. One participant in the observation group had >2 lines interocular acuity difference and was ineligible.

[c]Four participants (2%) in the observation group and 1 participant (<1%) in the patching group are missing the distance stereoacuity measurement.

[d]See protocol at www.pedig.net for details of exotropia classification. One participant (<1%) in the observation group is missing exotropia classification.

logMAR = logarithm of the Minimal Angle of Resolution; arcsec = seconds of arc; log arcsec = logarithm of seconds of arc; SD = standard deviation; AC/A = accommodative convergence/accommodation

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Table 4

Baseline Ocular Alignment According to Treatment Group

	Distance Alignment				Near Alignment			
	Observation N=183		Patching N=175		Observation N=183		Patching N=175	
	N	%	N	%	N	%	N	%
Deviation Type								
Constant exotropia	9	5	8	5	1	1	1	1
Intermittent exotropia	174	95	167	95	129	70	119	68
Exophoria	---	---	---	---	49	27	44	25
No exodeviation	---	---	---	---	4	2	11	6
Exotropia (Δ) by SPCT								
0 (no measurable tropia)[a]	48	26	50	29	108	59	108	62
1–9	15	8	18	10	23	13	27	15
10–14	18	10	12	7	21	11	11	6
16–18	30	16	29	17	13	7	12	7
20–25	57	31	47	27	14	8	9	5
30–35	13	7	15	9	4	2	5	3
40–50	2	1	4	2	0	0	3	2
Median	16		16		0		0	
Range	0 to 45		0 to 45		0 to 30		0 to 45	
Exodeviation (Δ) by PACT[b c**]								
No exodeviation (orthophoria)	---	---	---	---	6	3	7	4
1–9	---	---	---	---	19	10	31	18
10–14	7	4	11	6	49	27	45	26
16–18	34	19	33	19	32	17	24	14
20–25	101	55	87	50	52	28	48	27
30–35	35	19	39	22	21	11	15	9
40–45	5	3	5	3	4	2	5	3
≥50	1	1	0	0	0	0	0	0
Mean (SD)	23.3 (6.7)		23.6 (6.7)		18.0 (8.9)		16.7 (9.3)	

	Distance Alignment				Near Alignment			
	Observation N=183		Patching N=175		Observation N=183		Patching N=175	
	N	%	N	%	N	%	N	%
Range	10 to 50		10 to 45		0 to 45		−4 to 45	
Exotropia control score[23]								
No exodeviation	0	0	0	0	5	3	7	4
(0) No XT unless dissociated, recovers <1 sec	5	3	5	3	58	32	58	33
(1) No XT unless dissociated, recovers 1–5 sec	34	19	47	27	71	39	63	36
(2) No XT unless dissociated, recovers >5 sec	71	39	56	32	28	15	26	15
(3) XT <50% of 30-seconds	40	22	37	21	18	10	14	8
(4) XT >50% of 30-seconds	21	11	19	11	2	1	7	4
(5) Constant XT	12	7	11	6	1	1	0	0
Mean (SD)	2.4 (1.2)		2.3 (1.2)		1.1 (1.0)		1.1 (1.1)	

XT = Exotropia Δ - prism diopter

SPCT = Simultaneous Prism and Cover Test PACT = Prism and Alternate Cover Test

[a] ‘No measurable tropia’ includes participants who did not have a tropia during the exam, participants who had an exotropia not detectable by the cover/uncover test, and participants who had an exotropia that was not measurable because it was too brief, too small, or the participant was not cooperative enough to allow a simultaneous prism and cover test measurement.

[b] Prism and alternate cover test measurement at distance was required to be at least 10Δ for eligibility.

[c] One participant in the patching group had a 4Δ near esophoria at baseline and thus was considered −4Δ and was subsequently classified in the “no exodeviation” category.

--- indicates not applicable

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Table 5

Six-Month Primary Outcome According to Treatment Group

	AT 3-MONTH VISIT (INTERIM OUTCOME)		BY 6-MONTH VISIT (PRIMARY OUTCOME)[a]	
	Observation (N=162)	**Patching (N=158)**	**Observation (N=165)**	**Patching (N=159)**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Deterioration	5 (3.1)	1 (0.6)	10 (6.1)	1 (0.6)
Formal deterioration criteria met	4 (2.5)	1 (0.6)	7 (4.2)	1 (0.6)
Constant exotropia ≥10Δ at distance and near by SPCT	1 (0.6)[b]	0	1 (0.6)[b]	0
Stereoacuity worsening of ≥2 octaves	3 (1.9)	1 (0.6)	6 (3.6)	1 (0.6)
Both criteria	0	0	0	0
Started treatment without meeting deterioration criteria	1 (0.6)	0	3 (1.8)	0

[a]The 6-month primary outcome is based on deterioration at either the 3-month or 6-month visit.

[b]The participant who met the constant exotropia deterioration criterion had a tropia (30Δ at distance and 25Δ at near) yet had 40 arcsec of near stereoacuity; therefore, it is questionable whether the exotropia was truly constant (the masked examiner did not perform a protocol-specified cover/uncover test during stereoacuity testing to determine whether the tropia was present at that time).

SPCT = simultaneous prism and cover test; Δ = prism diopter; arcsec = seconds of arc

IXT3 – A Randomized Trial Evaluating Short-term Effectiveness of Overminus Lenses in Children 3 to 6 Years of Age with Intermittent Exotropia.

Citation: Pediatric Eye Disease Investigator Group. A Randomized Trial Evaluating Short-term Effectiveness of Overminus Lenses in Children 3 to 6 Years of Age with Intermittent Exotropia. Ophthalmology. Oct 2016;123(10):2127-36

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

A Randomized Trial Evaluating Short-term Effectiveness of Overminus Lenses in Children 3 to 6 Years of Age with Intermittent Exotropia

*Pediatric Eye Disease Investigator Group**
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Purpose: To evaluate the short-term effectiveness of overminus spectacles in improving control of childhood intermittent exotropia (IXT).

Design: Randomized, clinical trial.

Participants: A total of 58 children aged 3 to <7 years with IXT. Eligibility criteria included a distance control score of 2 or worse (mean of 3 measures during a single examination) on a scale of 0 (exophoria) to 5 (constant exotropia) and spherical equivalent refractive error between −6.00 diopters (D) and +1.00 D.

Methods: Children were randomly assigned to overminus spectacles (−2.50 D over cycloplegic refraction) or observation (non-overminus spectacles if needed or no spectacles) for 8 weeks.

Main Outcome Measures: The primary outcome was distance control score for each child (mean of 3 measures during a single examination) assessed by a masked examiner at 8 weeks. Outcome testing was conducted with children wearing their study spectacles or plano spectacles for the children in the observation group who did not need spectacles. The primary analysis compared mean 8-week distance control score between treatment groups using an analysis of covariance model that adjusted for baseline distance control, baseline near control, prestudy spectacle wear, and prior IXT treatment. Treatment side effects were evaluated using questionnaires completed by parents.

Results: At 8 weeks, mean distance control was better in the 27 children treated with overminus spectacles than in the 31 children who were observed without treatment (2.0 vs. 2.8 points, adjusted difference = −0.75 points favoring the overminus group; 2-sided 95% confidence interval, −1.42 to −0.07 points). Side effects of headaches, eyestrain, avoidance of near activities, and blur appeared similar between treatment groups.

Conclusions: In a pilot randomized clinical trial, overminus spectacles improved distance control at 8 weeks in children aged 3 to <7 years with IXT. A larger and longer randomized trial is warranted to assess the effectiveness of overminus spectacles in treating IXT, particularly the effect on control after overminus treatment has been discontinued. *Ophthalmology 2016;123:2127-2136 © 2016 by the American Academy of Ophthalmology.*

**Supplemental material is available at www.aaojournal.org.*

Intermittent exotropia (IXT), the most common form of childhood exotropia,[1−4] is characterized by normal ocular alignment some of the time and a manifest exotropia at other times. Although surgery is often considered for treatment, many cases of IXT are treated using nonsurgical interventions such as overminus lenses or occlusion.[5−8] Overminus lens therapy involves wearing full-time spectacles that have additional minus power over the cycloplegic refractive correction and is prescribed by some eye care providers to improve control and/or to reduce the angle of the exodeviation as a primary treatment or a temporizing treatment in young children before surgery or orthoptic therapy is considered.[9] One proposed mechanism for improvement with overminus lens therapy is that stimulation of accommodative convergence reduces the angle of exodeviation or triggers reflex convergence.[5,10] An alternative hypothesis is that fusional convergence is exerted to control the exodeviation, inducing convergence accommodation and distance blur, and that overminus lenses may allow clear distance vision, facilitating fusion.[11]

In some patients, overminus lenses alone appear to be successful in treating IXT, with eventual weaning of the overminus lenses to a point at which the IXT is well controlled in the regular refractive correction.[12,13] Nevertheless, previous studies of overminus lens therapy have been limited to retrospective case series without comparison

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groups and have varied in terms of methods used to determine the amount of overminus power, treatment duration, and outcome measures.[10,12–19] The objective of this pilot randomized trial was to evaluate the initial, short-term effectiveness of prescribing overminus lens therapy to improve control of IXT among children aged 3 to 6 years to determine whether a full-scale randomized clinical trial should be conducted to evaluate its long-term effectiveness, particularly after overminus treatment has been discontinued.

Methods

The study was supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health and was conducted by the Pediatric Eye Disease Investigator Group at 21 clinical sites according to the tenets of the Declaration of Helsinki. The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by institutional review boards, and a parent or guardian of each study participant gave written informed consent. An independent data and safety monitoring committee provided oversight. The study is listed on www.clinicaltrials.gov (NCT02223650, URL accessed February 9, 2016), and the full protocol is available at www.pedig.net (URL accessed February 9, 2016).

Eligibility Criteria

The study included children aged 3 to <7 years with spherical equivalent (SE) refractive error between −6.00 diopters (D) and +1.00 D inclusive and IXT meeting the following criteria: (1) intermittent or constant exotropia at distance (mean of 3 baseline assessments of distance control[18–20] ≥2 points) (Table 1); (2) IXT, exophoria, or orthophoria at near (at least 1 of 3 assessments of near control at the baseline visit ≤4 points); (3) distance exodeviation at least 15 prism diopters (Δ) measured by prism and alternate cover test (PACT); and (4) near deviation not exceeding the distance deviation by >10Δ by PACT (i.e., convergence insufficiency type IXT excluded). Prior nonsurgical treatment for IXT was not permitted within the 6 months preceding enrollment. Appropriate spectacle correction was required to be worn for at least 1 week before enrollment for children whose refractive error met certain prestudy criteria for correction (Table 2, criterion #11, available at www.aaojournal.org). Previous IXT treatment with spectacles overminused by ≥1.00 D SE was an exclusion criterion; however, low levels of uncorrected hyperopia (±1.0 D) were not considered overminus. Additional eligibility criteria are shown in Table 2 (available at www.aaojournal.org).

Enrollment Testing

At the enrollment visit, control of the exodeviation was measured at distance (6 m) and near (1/3 m) using the Office Control Score,[19,20] which ranges from 0 (phoria, best control) to 5 (constant exotropia, worst control) (Table 1). Because of the variability of single measures of control, we used the "triple control score,"[21,22] a mean of 3 measures obtained at specific time points during a 20- to 40-minute office examination.

After an initial control assessment, near stereoacuity was assessed using the Randot Preschool Stereoacuity test (Stereo Optical Co., Inc., Chicago, IL) at 40 cm, and magnitude of exodeviation was assessed at distance (6 m) and near (1/3 m) using the PACT. The control assessment was then performed a second time, followed by measurement of monocular distance visual acuity (VA) by a certified examiner using the Amblyopia Treatment Study HOTV[23,24] testing protocol and binocular near VA testing using the Amblyopia Treatment Study 4 test (Precision Vision, La Salle, IL). Finally, a third control assessment was performed. All 3 control assessments and the PACT were performed by the same study-certified examiner (a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist).

In addition to the clinical testing, the participant's parent completed a 7-item (Tables 3a-b, available at www.aaojournal.org) written survey of symptoms and problems that might be associated with over-minus spectacle wear, such as headaches and eye strain based on their observations in the past 2 weeks. Survey items were derived on the basis of expert opinion of pediatric ophthalmologists and optometrists on the study planning committee. The response options were a 5-point Likert-type scale based on frequency of observations: never = score of 0, almost never = 1, sometimes = 2, often = 3, and always = 4.

Randomization

After data were entered on the Pediatric Eye Disease Investigator Group website and eligibility was verified, participants were randomly assigned (using a permuted block design stratified by mean distance control score [2–<3, 3–<4, 4–5 points]) with equal probability to overminus treatment or observation.

Treatment Regimens

Participants assigned to the overminus group were prescribed spectacles with −2.50 D added to the sphere power of the cycloplegic refraction. Overminus spectacles were prescribed for all waking hours for 8 weeks, and no other IXT treatments were allowed during this time.

Participants assigned to the observation group received no treatment other than non-overminus refractive correction, if needed according to postrandomization correction criteria, which were more rigorous than the prestudy correction criteria in requiring correction of smaller amounts of astigmatism (>0.50 D) and anisometropia (>0.50 D). Observation group participants who did not need refractive correction were prescribed plano lens spectacles that were to be worn for outcome testing at the 8-week visit but were not to be worn in the interim. The sole purpose of the plano lens spectacles was to maintain masking of examiners for outcome testing at the 8-week visit by ensuring that all participants in both treatment groups would be tested while wearing spectacles.

Follow-up Visit

Follow-up consisted of a single visit 8 weeks (±2 weeks) after randomization. Before the clinical testing, parents completed the 7-item survey that asked about symptoms experienced by their child since the start of the study. An unmasked examiner assessed compliance with overminus spectacle wear. Compliance was judged to be excellent (glasses worn >75% of waking hours), good (51%–75%), fair (26%–50%), or poor (≤25%) on the basis of discussions with the parent. Afterward, clinical testing was performed in the same order as at enrollment with all participants

Table 1. Exotropia Control Assessment Procedure

Control of exodeviation will be measured at distance and near using the Office Control Score.[20]

- Distance (6 meters) − fixing on an accommodative target such as a video or reading optotype letters
- Near (1/3 meters) − fixing on Lang near-viewing stick or similar accommodative target

The scale below applies to both distance and near separately.

Intermittent Exotropia Control Scale

5 = constant exotropia
4 = exotropia >50% of the 30-seconds period before dissociation
3 = exotropia <50% of the 30-seconds period before dissociation
2 = no exotropia unless dissociated, recovers in >5 seconds
1 = no exotropia unless dissociated, recovers in 1−5 seconds
0 = no exotropia unless dissociated, recovers in <1 second (phoria)
Not applicable = no exodeviation present

Directions:

Step 1: Assessment before any dissociation: Levels 5 to 3 are assessed during a 30-second period of observation: first at distance fixation and then at near fixation for another 30-second period. Both distance and near are assessed before any dissociation (i.e., before step 2, when assessing control scores of 0, 1, and 2). If the participant is spontaneously tropic (score 3, 4, or 5) at a specified test distance, then step 2 (assessment after standard dissociation) is skipped at that specific test distance.

Step 2: Assessment with standardized dissociation: If no exotropia is observed during step 1 (i.e., the 30-second period of observation at the specified test distance), levels 2 to 0 are then assessed as the worst of 3 rapidly successive trials of dissociation:

1. An occluder is placed over the right eye for 10 seconds and then removed, measuring the length of time it takes for fusion to become reestablished.
2. The left eye is then occluded for a 10-seconds period (second assessment under dissociation) and the time to reestablish fusion is similarly measured.
3. A third assessment under dissociation is performed, covering the eye (for a 10-second period) that required the longest time to re-fuse.

The worse level of control observed after the three 10-second periods of occlusion should be recorded. Because the level under dissociation is recorded as the worst of the 3 assessments, if a score of 2 (>5 second recovery) is noted on the first or second dissociation, then subsequent dissociation(s) are not needed.

If the patient has a micro-esotropia by cover test but an exodeviation by PACT, the scale applies to the exodeviation.

PACT = prism and alternate cover test.

wearing spectacles (overminus spectacles for the overminus group; non-overminus or plano lens spectacles for the observation group). The 3 assessments of control and the PACT testing were performed by an examiner who was masked to the participant's treatment group. If the spectacles were not brought to the visit, the participant was tested in trial frames prepared by an unmasked examiner who covered the lens power markings with tape.

Statistical Methods

The planned sample size of 54 participants was not statistically calculated, but rather was a convenience sample expected to provide at least 50 participants (25 participants per group) for analysis after adjusting for up to 5% loss to follow-up. Nevertheless, a priori the study had 88% power to detect a treatment group difference in mean 8-week distance control score, assuming a true difference of −0.75 points or larger (overminus minus observation) with a standard deviation of 0.926 (based on prior IXT studies), and using a 1-sided test with alpha = 0.05.

The primary analysis was an intention-to-treat treatment group comparison of mean 8-week distance control using an analysis of covariance (ANCOVA) model that adjusted for baseline distance control. Prestudy spectacle wear, prior IXT treatment, and baseline near control were also included in the ANCOVA model to address potential confounding due to slight imbalances between treatment groups. A 1-sided hypothesis test using alpha = 0.05 was used to determine whether the overminus group had better 8-week mean distance control than the observation group in this pilot study to inform the decision whether to proceed with a full-scale, longer-term randomized trial. The treatment group difference in mean distance control also was calculated, along with a 2-sided 95% exact confidence interval (CI) to provide a range of likely values for the estimate. Two sensitivity analyses yielded similar results: (1) an analysis that excluded 1 participant not tested in study spectacles or plano glasses (an overminus group participant tested in trial frames with the overminus correction); and (2) a post hoc analysis that excluded 4 observation group participants who had (non-overminus) refractive correction prescribed for the first time or a change in (non-overminus) refractive correction at baseline (data not shown).

The secondary analysis was a treatment group comparison of the proportion of participants who demonstrated a *treatment response*, defined as 1 or more point improvement in mean distance control between baseline and the 8-week outcome examination. A 1-sided Barnard's exact test with alpha = 0.05 determined whether the overminus group had a higher proportion of participants with treatment response compared with the observation group in the pilot study to also inform the decision whether to proceed with a full-scale, longer-term treatment trial. The treatment group difference in proportion of participants with treatment response also was calculated along with the 2-sided exact 95% CI to provide a range of likely values for the estimate. The same 2 sensitivity analyses performed for the primary analysis were also performed and yielded similar results to the secondary analysis (data not shown). Unadjusted and adjusted logistic regression models were used to assess potential confounding due to treatment group imbalances in prestudy spectacle wear, prestudy treatment for IXT, and baseline near control.

Means for continuous 8-week outcomes of near exotropia control, PACT (distance and near), and stereoacuity were compared between treatment groups using ANCOVA models that included the baseline level of the outcome being evaluated and the additional baseline factors that were included in the primary analysis. For analysis, stereoacuity was converted from seconds of arc scores to log arcsec values (in parentheses) as follows: 40 (1.60), 60 (1.78), 100 (2.00), 200 (2.30), 400 (2.60), 800 (2.90); participants with no detectable (nil) stereoacuity were assigned a value of 1600 (3.20). Barnard's exact tests were used to compare treatment groups on post hoc outcomes of the proportion of participants with 8-week exotropia control scores that improved both $\geq$1 point and $\geq$2 points separately for each of distance and near. In addition, 8-week distance control mean, change from baseline, and proportion with improvement $\geq$1 point were tabulated for each treatment group stratified by baseline distance control (2−<3 points, 3−<4 points, 4−5 points). The primary analysis ANCOVA model also was used to assess the effect of baseline distance control on 8-week outcome in both treatment groups. In an exploratory analysis, we tested for interaction of continuous baseline distance control and treatment effect. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics

Between December 2014 and May 2015, 58 children were enrolled at 21 sites, with 31 participants assigned to observation and 27 participants assigned to overminus treatment. Mean age was 5.1 ($\pm$1.1) years, 36 (62%) were female, and 29 (50%) were white (Table 4). The mean control score at enrollment was 3.2 ($\pm$1.1) points at distance and 1.4 ($\pm$1.1) points at near (Table 5).

For the 31 participants assigned to the observation group, 6 (19%) continued their prestudy refractive correction, 1 (3%) was prescribed a change in refractive correction, 3 (10%) were prescribed refractive correction for the first time (2 participants did not require refractive correction for eligibility but did require refractive correction under the more rigorous postrandomization criteria; 1 participant was electively prescribed correction for minimal refractive error), and 21 (68%) were prescribed plano lenses to be brought to the 8-week visit (not to be worn in the interim).

Visit Completion

The 8-week visit was completed by all 31 participants in the observation group (all of whom completed the visit within the protocol-specified time window of 8$\pm$2 weeks) and by all 27 participants in the overminus group (24 [89%] of whom completed the visit within the protocol-specified time window). A masked examiner assessed the primary and secondary outcomes in all cases.

Compliance with Overminus Spectacle Wear

In the overminus group, potentially delayed receipt of overminus spectacles and the timing of the 8-week outcome visit allowed for a variable number of weeks of possible spectacle wear immediately preceding the outcome examination: 4 to <5 weeks in 4 participants (15%), 5 to <6 weeks in 3 participants (11%), 6 to <7 weeks in 4 participants (15%), 7 to <8 weeks in 11 participants (41%), and $\geq$8 weeks in 5 participants (19%) (mean, 7 weeks; range, 4−11 weeks).

At the 8-week visit, compliance with overminus spectacles in the overminus group was judged to be excellent in 20 participants (74%), good in 4 participants (15%), fair in 1 participant (4%), and poor in 2 participants (7%).

Refractive Correction for Outcome Testing

In the overminus group, the 8-week outcome was assessed for 26 participants (96%) while wearing their overminus spectacles and for 1 participant (4%) while wearing trial frames with the overminus correction. In the observation group, the 8-week outcome was assessed for 10 participants (33%) while wearing spectacles with refractive correction and for 21 participants (68%) while wearing plano lens spectacles, because they did not require refractive correction.

Efficacy Analyses

The primary outcome of adjusted 8-week mean distance control was 2.0 points in the 27 participants in the overminus group versus 2.8 points in the 31 participants in the observation group ($P = 0.01$ for 1-sided test of the hypothesis that mean distance control is better in the overminus group vs. the observation group), supporting development of a full-scale longer-term randomized trial based on our a priori criterion of $P \leq 0.05$. The adjusted difference in mean 8-week control was −0.75 points (2-sided 95% CI, −1.42 to −0.07 points), favoring the overminus group (Table 6, Fig 1). The 8-week distance control improved $\geq$1 point from baseline in 16 participants (59%) in the overminus group versus 12 participants (39%) in the observation group ($P = 0.07$ for 1-sided test of the hypothesis that the overminus group had a higher proportion of participants with treatment response compared with the observation group), supporting development of a full-scale longer-term randomized trial based on our a priori criterion of $\geq$20% more participants with treatment response in the overminus group. The treatment group difference in the proportion of participants with treatment response was 21% (2-sided 95% CI, −6 to 45%). Adjusted and unadjusted exact logistic regression models yielded similar results.

In both treatment groups, the 8-week mean distance control improvement was greater in participants who had poorer distance control at baseline (Table 7). There was some suggestion that the magnitude of the treatment difference (favoring overminus treatment) was greater in participants with poorer baseline distance control ($P = 0.07$ for interaction).

The PACT at near at 8 weeks was 12.8 Δ in the overminus group versus 16.9 Δ in the observation group (baseline adjusted difference = −4.2 Δ [−7.4 to −1.1 Δ]) (Table 8). The treatment groups were not different with respect to 8-week control at near, PACT at distance, or stereoacuity at near (Table 8).

Safety and Tolerability

In regard to possible adverse effects of treatment, 1 child in the overminus group developed an esodeviation of 3 Δ at near (whether it was esophoria or esotropia was not recorded), although this child had no reduction in stereoacuity from baseline (Table 9, available at www.aaojournal.org). Two participants in the observation group and 2 participants in the overminus group had reduced monocular distance VA of 2 or more lines in 1 eye at 8 weeks and 1 participant in the observation group had reduced binocular near VA of 2 lines at 8 weeks (Table 9, available at www.aaojournal.org). Parent-reported symptoms

Table 4. Baseline Demographic and Clinical Characteristics by Treatment Group (N = 58)

	Observation (N = 31)		Overminus (N = 27)	
	N	%	N	%
Sex: Female	18	58	18	67
Race/ethnicity				
White	15	48	14	52
Black/African American	4	13	2	7
Hispanic or Latino	9	29	6	22
Asian	3	10	5	19
Age at randomization, yrs				
3−<4	3	10	7	26
4−<5	11	35	4	15
5−<6	10	32	9	33
6−<7	7	23	7	26
Mean (SD)	5.2 (1)		5.1 (1.2)	
Range	3.4−6.8		3.0−7.0	
Refractive error in more myopic eye* (SE, D)				
>+0.50 to +1.00	15	48	13	48
0 to +0.50	9	29	5	19
<0 to >−0.50	1	3	2	7
−0.50 to >−1.00	1	3	4	15
−1.00 to >−1.50	0	0	1	4
−1.50 to >−2.00	0	0	1	4
−2.00 to >−2.50	2	6	0	0
−2.50 to >−3.00	2	6	0	0
≤−3.00	1	3	1	4
Median	0.38		0.25	
Mean (SD)	−0.04 (1.47)		−0.05 (1.40)	
Range	−5.25 to +1.00		−6.00 to +1.00	
Spectacle wear (prestudy)†	7	23	10	37
Prior IXT treatment	3	10	6	22
Patching	2	6	6	22
Home antisuppression treatment	1	3	0	0
Preschool Randot near stereoacuity, arcsec (log arcsec)‡				
40” (1.6 log arcsec)	4	13	3	12
60” (1.78 log arcsec)	9	30	4	15
100” (2.0 log arcsec)	7	23	6	23
200” (2.3 log arcsec)	1	3	2	8
400” (2.6 log arcsec)	4	13	4	15
800” (2.9 log arcsec)	1	3	2	8
Nil (3.1 log arcsec)	4	13	5	19
Median (log arcsec)	2.00		2.15	
Mean (SD) (log arcsec)	2.16 (0.54)		2.34 (0.57)	
Range (log arcsec)	1.60−3.20		1.60−3.20	
AC/A ratio§				
<2.5	13	42	12	44
2.5−6.0	15	48	12	44
>6.0	3	10	3	11

AC/A = accommodative convergence over accommodation; D = diopters; IXT = intermittent exotropia; SD = standard deviation; SE = spherical equivalent.
*More myopic eye refers to the eye with the numerically lowest SE refractive error.
†After randomization, for the 31 participants assigned to the observation group, 6 (19%) continued their prestudy refractive correction, 1 (3%) was prescribed a change in refractive correction, 3 (10%) were prescribed refractive correction for the first time (2 participants did not require refractive correction for eligibility but did require refractive correction under the more rigorous postrandomization criteria; 1 participant was electively prescribed correction for minimal refractive error), and 21 (68%) were prescribed plano lenses to be brought to the 8-wk visit (not to be worn in the interim).
‡Randot Preschool stereoacuity is missing for 1 participant in the observation group and 1 participant in the overminus group because they did not understand the test (i.e., failed the pretest).
§Accommodative convergence over accommodation ratio calculated by taking the difference between the distance (6 m) PACT measurements with the participant wearing habitual correction and with the participant wearing −2.00 D lenses over the habitual correction, and dividing the difference by 2.

were infrequent and appeared similar between treatment groups (Table 3a, available at www.aaojournal.org), and spectacle-related issues did not appear to occur more frequently in the 27 overminus group participants compared with the 10 observation group participants who were prescribed spectacles (Table 3b, available at www.aaojournal.org).

Table 5. Baseline Exotropia Control and Angle Magnitude by Treatment Group (N=58)

	Distance Alignment				Near Alignment			
	Observation (N = 31)		Overminus (N = 27)		Observation (N = 31)		Overminus (N = 27)	
	N	%	N	%	N	%	N	%
Exotropia control*								
0−<1	–	–	–	–	11	35	7	26
1−<2	–	–	–	–	9	29	12	44
2−<3	13	42	12	44	6	19	5	19
3−<4	7	23	6	22	3	10	2	7
4−5	1	35	9	33	2	6	1	4
Mean (SD)	3.2 (1.1)		3.2 (1.1)		1.5 (1.2)		1.3 (1.0)	
Range	2−5		2−5		0−4		0−4	
PACT exodeviation (Δ)† (in habitual correction)								
No exodeviation (orthophoria)	–	–	–	–	0	0	0	0
1−9	–	–	–	–	3	10	2	7
10−15	0	0	1	4	11	35	10	37
16−18	3	10	2	7	4	13	4	15
20−25	19	61	18	67	10	32	8	30
30−35	8	26	5	19	2	6	2	7
40−45	1	3	1	4	1	3	1	4
Mean (SD)	25 (6)		24 (7)		18 (8)		18 (8)	
Range	16−45		15−45		6−45		6−40	

—— = not applicable; PACT = prism and alternate cover test; Δ = prism diopter; SD = standard deviation.
*Mean of 3 assessments performed throughout the examination. Mean distance exotropia control of 2 points or greater (worse) was required for eligibility. Mean near exotropia control of less than 5 points (i.e., could not be constant on all 3 of the measures) was required for eligibility.
†The PACT at distance was required to be at least 15Δ for eligibility. In addition, near deviation could not exceed distance deviation by more than 10Δ by PACT for eligibility (i.e., convergence insufficiency type IXT was excluded).

Table 6. Exotropia Control at 8-Week Outcome (Average of 3 Measurements) (N = 58)*

	Distance Alignment				Near Alignment			
	Observation (N = 31)		Overminus (N = 27)		Observation (N = 31)		Overminus (N = 27)	
	N	%	N	%	N	%	N	%
8-wk control score (points)								
0−<1	1	3	4	15	10	32	15	56
1−<2	7	23	11	41	13	42	7	26
2−<3	10	32	5	19	3	10	2	7
3−<4	3	10	1	4	5	16	2	7
4−5	10	32	6	22	0	0	1	4
Mean (SD)	2.8 (1.4)		2.0 (1.4)		1.2 (1.1)		0.9 (1.2)	
Range	0.3−5.0		0.0−5.0		0.0−3.7		0.0−4.0	
Difference in means (2-sided 95% CI)	−0.75 (−1.42 to −0.07)*				−0.24 (−0.68 to 0.19)*			
Change from baseline to 8 wks (points)†								
Mean (SD)	−0.4 (1.3)		−1.2 (1.8)		−0.3 (1.1)		−0.4 (0.9)	
Range	−3.0 to 2.3		−5.0 to 3.0		−3.7 to 1.7		−2.0 to 2.0	
Improved ≥1 point‡	12	39	16	59	8	26	7	26
Difference (2-sided 95% CI)	21% (−6 to 45)				0.001% (−23 to 24)			
Improved ≥2 points§	4	13	9	33	2	6	3	11
Difference (2-sided 95% CI)	20% (−2 to 44)				5% (−12 to 24)			

CI = confidence interval; SD = standard deviation.
*Difference in mean distance control (overminus−observation) and 95% CIs are from analysis of covariance (ANCOVA) model adjusting for baseline distance control, baseline near control, prestudy spectacle wear, and prestudy treatment for IXT. Difference in mean near control (overminus−observation) and 95% CIs from ANCOVA model adjusting for baseline near control, prestudy spectacle wear, and prestudy treatment for IXT. *P* values for 1-sided treatment group comparisons = 0.01 for distance control and 0.14 for near control.
†Change is calculated as 8 wks minus baseline so negative change = improvement. Maximum range of change possible is −5 (improvement) points to 3 points (worsening) for distance control and −4.67 (improvement) to 5 points (worsening) for near control.
‡Control improvement of ≥1 points between baseline and 8 wks is the a priori definition of treatment response. *P* values for 1-sided treatment group comparisons = 0.07 for distance control and 0.54 for near control.
§Control improvement of ≥2 points is a post hoc additional outcome of interest. *P* values for 1-sided treatment group comparisons = 0.04 for distance control and 0.33 for near control.

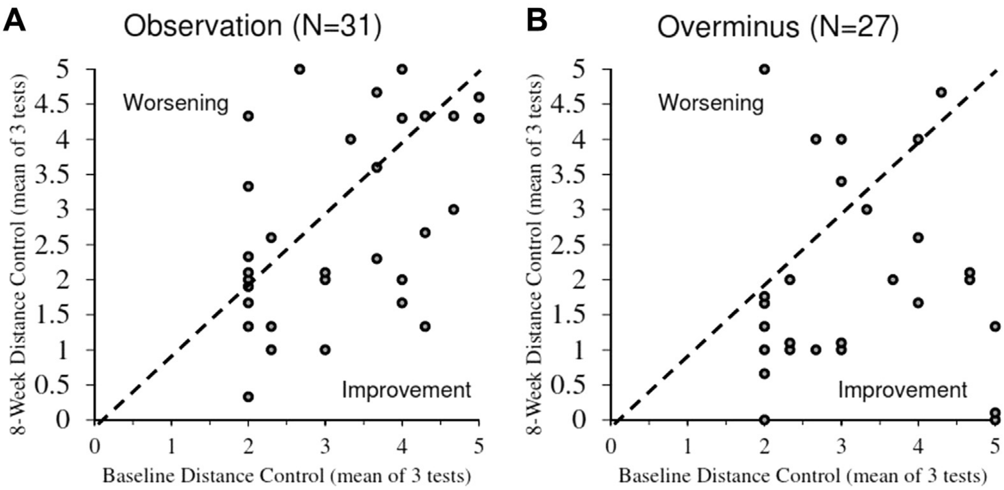

Figure 1. Baseline versus 8-week distance exotropia control for (**A**) observation group subjects (N = 31) and (**B**) overminus group subjects (N = 27). A few points have been offset slightly (±0.1 point) to aid visibility.

Discussion

We evaluated the short-term effectiveness of overminus spectacles (−2.50 D over the cycloplegic refraction) compared with observation (usual spectacle correction, if needed) for improving distance exotropia control in children aged 3 to 6 years with IXT. The mean distance exotropia control score 8 weeks after randomization was better in the overminus group than in the observation group (2.0 vs. 2.8 points), and 21% more of the overminus group than in the observation group showed treatment response, defined as ≥1 point improvement in distance control (59% vs. 39%, albeit not statistically significant).

We are not aware of any prospective randomized clinical trial that has compared overminus spectacles with observation in children with IXT. A treatment effect of overminus lens therapy for IXT has been reported in several retrospective studies without comparison groups.[10,12−19] In these previous studies, the amount of overminus prescribed ranged from 0.50 D to 5.00 D. The 2 most common prescribing approaches were (1) to prescribe a fixed amount of overminus based on refractive error and/or age[10,12,15] and (2) to select an initial amount of overminus and increase it incrementally until a certain level of control of IXT was achieved.[13,14,16] In addition, treatment duration varied within each study. These previous studies reported overminus treatment to be effective in improving control of IXT, defined as no manifest tropia,[13,15,16,18] reduction in Newcastle control score,[19] or presence of fusion.[14] The results of our pilot study, incorporating randomization of treatment assignment, standardization of visit timing, and masking of outcome assessment, also support the finding of improved control of IXT with overminus lens treatment at 8 weeks.

In our pilot randomized clinical trial, we chose 2.50 D as the amount of overminus because it allowed the final power of the spectacles to be at least −1.50 D SE, while maintaining a constant accommodative demand in all participants regardless of their underlying cycloplegic refractive error. Overall, participants showed good compliance and tolerance of this dose of overminus, based on parental report. The side effects of headaches, blur, eye strain, and avoidance of near work appeared to be similar between the overminus and observation groups, which suggest that the dosage of 2.50 D overminus was well tolerated.

We performed secondary analyses to assess the effectiveness of overminus based on the level of baseline distance control. Of note, children with poorer baseline mean

Table 7. Distance Exotropia Control at 8 Weeks According to Baseline Distance Control (N = 58)

Baseline Distance Control Score (Points)	8-Week Control Score (Points)				Change in Control from Baseline to 8 Weeks (Points)*				Treatment Response at 8 Weeks (Control Improved ≥1 Point)			
	Observation		*Overminus*		*Observation*		*Overminus*		*Observation*		*Overminus*	
	N	*Mean*	*N*	*Mean*	*N*	*Mean*	*N*	*Mean*	*N*	*N (%)*	*N*	*N (%)*
2−<3	13	2.3	12	1.7	13	0.1	12	−0.5	13	3 (23)	12	6 (50)
3−<4	7	2.8	6	2.5	7	−0.5	6	−0.7	7	4 (57)	6	3 (50)
4−5	11	3.4	9	2.0	11	−1.0	9	−2.5	11	5 (45)	9	7 (78)

*Change is calculated as 8 wks minus baseline so negative change = improvement. Maximum range of change possible is −5 (improvement) points to 3 points (worsening) for distance control and −4.67 (improvement) to 5 points (worsening) for near control.

Table 8. Eight-Week Stereoacuity and Prism and Alternate Cover Test Outcomes According to Treatment Group (N = 58)

	Observation (N = 31)			Overminus (N = 27)		
	N		%	N		%
Randot Preschool Stereoacuity*						
At 8 wks						
40”–60”	13		43	9		33
100”–400”	10		33	14		52
800” or nil	7		23	4		15
Median		2.0			2.0	
Mean (SD) (log arcsec)†		2.2 (0.6)			2.2 (0.5)	
Range (log arcsec)		1.6–3.2			1.6–3.2	
Difference in means (95% CI)‡			−0.1 (−0.3 to 0.1)			
Change between baseline and 8 wks§						
Mean (SD) (log arcsec)		0.0 (0.4)			−0.1 (0.3)	
Range (log arcsec)		−1.3 to 0.6			−1.2 to 0.6	
PACT exodeviation at distance (Δ)						
At 8 wks						
No exodeviation (orthophoria)	0		0	0		0
1–9	1		3	3		11
10–15	3		10	5		19
16–18	3		10	4		15
20–25	15		48	11		41
30–35	9		29	2		7
40–45	0		0	0		0
≥50	0		0	2		7
Mean		23.0 (6.3)			21.1 (11.2)	
Range		6–30			4–50	
Difference in means (95% CI)‖			−1.9 (−5.6 to 1.8)			
Change between baseline and 8 wks¶						
Mean (SD)		−1.8 (5.4)			−3.3 (9.6)	
Range		−15 to 5			−19 to 25	
PACT exodeviation at near (Δ)						
At 8 wks						
No exodeviation (orthophoria)	1		3	2		7
1–9	6		19	5		19
10–15	4		13	9		33
16–18	6		19	3		11
20–25	12		39	6		22
30–35	2		6	1		4
40–45	0		0	0		0
≥50	0		0	0		0
Esodeviation#	0		0	1		4
Mean (SD)		16.9 (8.4)			12.8 (8.3)	
Range		0–30			−3 to 30	
Difference in means (95% CI)‖			−4.7 (−7.7 to −1.7)			
Change between baseline and 8 wks¶						
Mean (SD)		−0.6 (6.6)			−5.0 (6.9)	
Range		−15 to 13			−20 to 10	

CI = confidence interval; PACT = prism and alternate cover test; SD = standard deviation.
*Outcome stereoacuity is missing for 1 observation group participant who failed the pretest.
†Logarc second stereoacuity values range from 1.6 log arcsec (40”) to 3.2 (nil), so lower values are better.
‡Difference in means (overminus−observation) and 95% CIs from ANCOVA models that adjust for baseline stereoacuity, baseline near control, prestudy spectacle wear, and prestudy treatment for IXT.
§Change in stereoacuity is calculated as 8 wks minus baseline, so negative change = improvement. Change in stereoacuity is missing for 1 observation group participant who failed the pretest at baseline and 8 wks, and 1 overminus group participant who failed the pretest at baseline.
‖Difference in means and 95% CIs from ANCOVA models that adjust for baseline PACT (baseline distance PACT for the distance PACT outcome; baseline near PACT for the near PACT outcome), baseline near control, prestudy spectacle wear, and prestudy treatment for IXT.
¶Change is PACT is calculated as 8 wks minus baseline, so negative change = improvement.
#One participant in the overminus group had the deviation at near change from 12 PD exodeviation at baseline to 3 PD esodeviation at 8 wks. During the same period, exodeviation at distance for this participant changed from 20 PD to 12 PD and stereoacuity at near changed from 100 arcsec to 60 arcsec.

distance control scores showed more improvement in their distance control than children with better mean distance control. Although this greater response in children with poor baseline control may be partly due to regression to the mean and having more room for improvement, the same magnitude of response was not seen in the observation group, suggesting that this greater effect of overminus treatment on children with poorer control may be real. Nevertheless, this preliminary observation suggesting greater effectiveness of overminus treatment for very poorly controlled IXT needs to be interpreted with caution because of the small sample sizes in subgroups.

Study Limitations

By design, our current study was a pilot randomized clinical trial with a small sample size and only 8 weeks of follow-up. We do not know if the treatment effect would persist after overminus lenses are replaced with usual spectacle correction. Our estimates of improved control with overminus treatment may be overestimates, given the high test–retest variability of control (due in part to inherent variability of the condition) combined with a distance control score eligibility requirement of 2 points or worse (expected to have resulted in some improvement due solely to regression to the mean).[21,22,25] Nevertheless, we would expect these factors would affect the randomized groups equally and therefore would not influence our primary finding that overminus treatment improved distance control compared with observation. Our study has a number of strengths over previous retrospective reviews and case series. First, we incorporated randomization of treatment assignment. Second, all 58 participants returned for the 8-week follow-up. In addition, participants were evaluated using standardized measures by certified examiners who were masked to treatment assignment by having all participants wear glasses for the outcome examination, including plano spectacles for testing children in the observation group who did not wear refractive correction.

Conclusion

In this pilot randomized trial, we found that overminus spectacles improved distance control at 8 weeks in children aged 3 to 6 years with IXT. A larger and longer randomized treatment trial is warranted to assess the effectiveness of overminus spectacles and to determine whether there is a lasting effect on control of IXT after overminus treatment has been discontinued.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
ANCOVA = analysis of covariance; **CI** = confidence interval; **D** = diopters; **IXT** = intermittent exotropia; **PACT** = prism and alternate cover test; **Δ** = prism diopters; **SE** = spherical equivalent; **VA** = visual acuity.

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Overminus Lens Therapy for Children 3 to 10 Years of Age With Intermittent Exotropia
A Randomized Clinical Trial

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IMPORTANCE This is the first large-scale randomized clinical trial evaluating the effectiveness and safety of overminus spectacle therapy for treatment of intermittent exotropia (IXT).

OBJECTIVE To evaluate the effectiveness of overminus spectacles to improve distance IXT control.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial conducted at 56 clinical sites between January 2017 and January 2019 associated with the Pediatric Eye Disease Investigator Group enrolled 386 children aged 3 to 10 years with IXT, a mean distance control score of 2 or worse, and a refractive error between 1.00 and −6.00 diopters (D). Data analysis was performed from February to December 2020.

INTERVENTIONS Participants were randomly assigned to overminus spectacle therapy (−2.50 D for 12 months, then −1.25 D for 3 months, followed by nonoverminus spectacles for 3 months) or to nonoverminus spectacle use.

MAIN OUTCOMES AND MEASURES Primary and secondary outcomes were the mean distance IXT control scores of participants examined after 12 months of treatment (primary outcome) and at 18 months (3 months after treatment ended) assessed by an examiner masked to treatment group. Change in refractive error from baseline to 12 months was compared between groups. Analyses were performed using the intention-to-treat population.

RESULTS The mean (SD) age of 196 participants randomized to overminus therapy and 190 participants randomized to nonoverminus treatment was 6.3 (2.1) years, and 226 (59%) were female. Mean distance control at 12 months was better in participants treated with overminus spectacles than with nonoverminus spectacles (1.8 vs 2.8 points; adjusted difference, −0.8; 95% CI, −1.0 to −0.5; *P* < .001). At 18 months, there was little or no difference in mean distance control between overminus and nonoverminus groups (2.4 vs 2.7 points; adjusted difference, −0.2; 95% CI, −0.5 to 0.04; *P* = .09). Myopic shift from baseline to 12 months was greater in the overminus than the nonoverminus group (−0.42 D vs −0.04 D; adjusted difference, −0.37 D; 95% CI, −0.49 to −0.26 D; *P* < .001), with 33 of 189 children (17%) in the overminus group vs 2 of 169 (1%) in the nonoverminus group having a shift higher than 1.00 D.

CONCLUSIONS AND RELEVANCE Children 3 to 10 years of age had improved distance exotropia control when assessed wearing overminus spectacles after 12 months of overminus treatment; however, this treatment was associated with increased myopic shift. The beneficial effect of overminus lens therapy on distance exotropia control was not maintained after treatment was tapered off for 3 months and children were examined 3 months later.

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Invited Commentary

Multimedia

Supplemental content

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Overminus lens therapy is a nonsurgical treatment option for childhood intermittent exotropia (IXT), in which an optical correction with more minus power than the cycloplegic refractive error is worn.[1,2] Overminus lenses are typically used as a temporary treatment to improve control of IXT in young children before considering surgery[3-7] or orthoptics.[4,7] Some authors have reported success in maintaining good control and binocular function after gradually decreasing the strength of the overminus lenses over time and ultimately discontinuing the overminus lenses.[5,6]

Most previous studies of overminus spectacles are retrospective case series or small prospective studies without comparison groups.[3-10] However, a previous pilot randomized clinical trial found that, compared with observation, short-term (8-week) distance IXT control improved while wearing overminus spectacles of −2.50 diopters (D).[11]

The present randomized clinical trial of children 3 to 10 years of age evaluated the effectiveness of overminus lens therapy for improving distance IXT control while wearing overminus lenses, after 12 months of overminus treatment, and 3 months after the overminus lens treatment was tapered off. In addition, potential adverse effects on refractive error and symptoms associated with use of overminus spectacles were monitored.

Key Points

Question Does overminus lens therapy improve distance control in children with intermittent exotropia?

Findings This randomized clinical trial found that mean distance exotropia control was significantly better among 386 children aged 3 to 10 years treated with overminus spectacles vs nonoverminus spectacles for 12 months; however, after weaning off overminus spectacles, there was little or no difference in distance control between groups. Myopic shift was approximately one-third diopter greater in the overminus than in the nonoverminus group.

Meaning Overminus lens therapy improved distance exotropia control in children 3 to 10 years of age but was associated with greater myopic shift, and the improved control did not persist after overminus treatment was discontinued.

Methods

The study was conducted according to the tenets of the Declaration of Helsinki[12] by the Pediatric Eye Disease Investigator Group at 56 academic- and community-based clinical sites. An independent data and safety monitoring committee provided oversight. The study was designed in 2016 and is listed on ClinicalTrials.gov.[13] This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The full trial protocol is available in Supplement 1. The protocol and informed consent forms, compliant with the Health Insurance Portability and Accountability Act, were approved by institutional review boards for each site, and a parent or guardian (hereafter referred to as parent) of each study participant gave written informed consent. Study participants received $50 compensation per visit.

Enrollment

Eligible children were 3 to younger than 11 years of age with cycloplegic spherical equivalent (SE) refractive error between −6.00 D and 1.00 D inclusive, and IXT of moderate or poor control and meeting specified magnitude criteria (**Box**). Additional eligibility criteria are shown in the Box.

Testing at enrollment was performed through the participant's habitual correction. Control of the exodeviation was measured at distance (6 m) and near (0.3 m) using the IXT Office Control Score,[14] which ranges from 0 (phoria) to 5 (constant exotropia) (eTable 1 in Supplement 2). Control levels 3 to 5 were assigned based on the duration of manifest exotropia during a 30-second period before any dissociation. If no exotropia was observed during this period, control levels 0 to 2 were assigned based on the longest time to reestablishing fusion following 3 consecutive 10-second periods of dissociation. Control was measured at the beginning, middle, and end (3 tests total) of a 20- to 40-minute office examination, and the mean level was used.[15-17] The following tests were performed sequentially by the same study-certified examiner (pediatric optometrist, pediatric ophthalmologist, or certified orthoptist): first control assessment; stereoacuity using the Randot Preschool Stereoacuity test (Stereo Optical Co, Inc) at 40 cm; second control assessment; cover-uncover test; prism and alternate cover test (PACT) at distance and near; PACT retesting at distance with −2.00 D lenses over the habitual correction to assess the ratio of accommodative convergence to accommodation; and third control assessment. Distance visual acuity was assessed using an optotype method. Cycloplegic refraction was performed within 2 months prior to enrollment; cycloplegic autorefraction was also performed at clinical sites that had an autorefractor.

In addition, each child completed an IXT Symptom Survey[18] to assess IXT-related symptoms, and the parent completed a 7-item Spectacles Symptom Survey to assess issues related to overminus spectacle wear (eg, headache, eyestrain, and looking over glasses). Health-related quality of life was assessed using the Intermittent Exotropia Questionnaire (IXTQ)[19,20] for each child (separate version for 5- to 7-year-old children vs ≥8-year-old children) and parent. Participants were randomly assigned 1:1 using a permuted block design stratified by site and distance control (2 to <3, 3 to <4, 4 to 5 points), to either overminus or nonoverminus spectacles.

Treatment Regimens

Participants assigned to the overminus group were prescribed spectacles with −2.50 D added to the spherical power of the cycloplegic refraction to be worn for 12 months. Participants were then weaned by wearing −1.25 D overminus lenses for 3 months, before discontinuing overminus lenses and wearing nonoverminus spectacles until the 18-month visit.

Participants assigned to the nonoverminus group were prescribed spectacles that fully corrected astigmatism, anisometropia, and myopia based on the cycloplegic refraction to be worn for 18 months. For participants with SE hyperopia, the

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Box. Eligibility Criteria

Inclusion criteria

Aged 3 to <11 y

Intermittent exotropia (manifest deviation) meeting all of the following criteria:

- At distance: intermittent exotropia or constant exotropia
  - Mean distance control score of ≥2 points (mean of 3 assessments during the examination)
- At near: intermittent exotropia, exophoria, or orthophoria
  - Individual cannot have a score of 5 points on all 3 near assessments of control
- Exodeviation at least 15Δ at distance measured by the prism and alternate cover test
- Near deviation does not exceed distance deviation by more than 10Δ by prism and alternate cover test (convergence insufficiency type intermittent exotropia excluded)

Distance visual acuity (any optotype method) in each eye of 0.4 logMAR (20/50) or better if aged 3 to <4 y and 0.3 logMAR (20/40) or better if ≥4 y

Interocular difference of distance visual acuity ≤0.2 logMAR (2 lines on a logMAR chart)

Refractive error between −6.00-D spherical equivalents (SEs) and 1.00-D SEs (inclusive) in the most myopic or least hyperopic eye based on a cycloplegic refraction performed within the last 2 mo or at the end of the enrollment examination

If refractive error (based on cycloplegic refraction performed within last 2 mo or at the end of the enrollment examination) meets any of the following criteria, then prestudy spectacles are required and must have been worn for at least 1 wk prior to enrollment:

- SE anisometropia ≥1.00 D
- Astigmatism ≥1.50 D in either eye
- SE myopia ≥−1.00 D in either eye

Prestudy refractive correction, if worn, must meet the following criteria relative to the cycloplegic refraction performed within last 2 mo or at the end of the enrollment examination:

- SE anisometropia must be corrected within <1.00 D of the SE anisometropic difference
- Astigmatism must be corrected within <1.00 D of full magnitude; axis must be within 10°
- SE of spectacles must not meet the definition of substantial overminus (see exclusion criteria)

Gestational age ≥32 wk

Birth weight >1500 g

Parent understands the protocol and is willing to accept randomization to overminus spectacles or nonoverminus spectacles

Parent has home telephone (or access to telephone) and is willing to be contacted by Jaeb Center for Health Research staff and investigator's site staff

Relocation outside of area of an active Pediatric Eye Disease Investigator Group site within next 18 mo is not anticipated

Exclusion Criteria

Treatment of intermittent exotropia or amblyopia (other than refractive correction) within the last 4 wk, including vision therapy, patching, atropine, or other penalization

(continued)

Box. (continued)

Current contact lens wear

Substantial deliberate overminus treatment within the last 6 mo, defined as spectacles with an overminus of >1.00-D SEs than the cycloplegic refractive error (within 2 mo or at the end of the enrollment examination)

Prior strabismus, intraocular, or refractive surgery (including botulinum toxin injection)

Abnormality of the cornea, lens, or central retina

Down syndrome or cerebral palsy

Severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Children with mild speech delays or reading or learning disabilities are not excluded

Any disease known to affect accommodation, vergence, and ocular motility such as multiple sclerosis, Graves orbitopathy, dysautonomia, myasthenia gravis, or current use of atropine for amblyopia

Antiseizure medications (eg, carbamazepine [Tegretol, Carbatrol, Epitol, or Equetro], diazepam [Valium or Diastat], clobazam [Frisium or Onfi], clonazepam [Klonopin], lorazepam [Ativan], ethosuximide [Zarontin], felbamate [Felbatol], lacosamide [VIMPAT], gabapentin [Neurontin], oxcarbazepine [Oxtellar XR or Trileptal], phenobarbital, phenytoin [Dilantin or Phenytek], pregabalin [Lyrica], tiagabine [Gabitril], topiramate [Topamax], valproate [Depakote], zonisamide [Zonegran], or vigabatrin [Sabril])

Abbreviations: D, diopters; Δ, prism diopters.

sphere power that resulted in a SE plano lens were prescribed for the less hyperopic eye, with symmetrical reduction in the fellow eye.

To keep participants masked, the spectacle prescription was sealed in an envelope, and spectacle lenses were changed in both treatment groups at 12 and 15 months. In both treatment groups, spectacles were worn full time. No other IXT treatments were allowed unless the participant met motor or stereo deterioration criteria (eTable 2 in Supplement 2), after which treatment was at investigator discretion.

Early Discontinuation of Overminus Lens Therapy

On observing greater myopic shift in the overminus group, the data and safety monitoring committee discontinued overminus lens treatment in November 2019. When implemented in December 2019, the study had completed 345 (89%) 12-month visits, 303 (78%) 15-month visits, and 250 (65%) 18-month visits.

Follow-up Visits

Follow-up visits occurred at 6, 12 (primary outcome), 15, and 18 months (secondary outcome) (±1 month) after randomization. Telephone calls were completed at 1, 3, 9, 13, and 16 months after randomization to verify receipt of new spectacles and to maintain rapport with the family.

At each follow-up visit, the spectacle prescription was verified, and adherence with spectacle wear was rated based on parental report of the percentage of wear time during waking hours: excellent (>75%), good (51%-75%), fair (26%-50%), or poor (≤25%). Participants and parents then completed the

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symptom and IXTQ surveys. With participants wearing their current (ie, study) spectacles, an examiner masked to treatment group measured near stereoacuity, performed 3 IXT control assessments (at the beginning, middle, and end of the masked examination) at distance and near, the cover-uncover test, and the PACT at distance and near, in the order described for enrollment. If near stereoacuity had worsened by 2 or more octaves from baseline or to nil, it was retested (eTable 2 in Supplement 2). If stereoacuity remained decreased, it was then retested on a subsequent day (within a month) to confirm or refute meeting stereo deterioration criteria. A cycloplegic refraction was performed by an unmasked examiner at 12-month visits; cycloplegic autorefraction was also performed when available at the clinical site.

Statistical Analysis

Assuming an SD of 1.8 points in the IXT control score based on a prior pilot study by members of our group,[11] 2-sided α = .05, a power of 90%, and up to 10% loss to follow-up, a sample size of 384 (192 per group) was needed to detect a difference in mean 12-month and mean 18-month distance control scores (overminus − nonoverminus), assuming the true mean difference was −0.65 points or larger.

The primary analysis was an intention-to-treat treatment group comparison of mean distance control score after 12 months of treatment using analysis of covariance (ANCOVA) adjusting for baseline values of distance control, age, refractive error, and distance (eAppendix in Supplement 2). Multiple imputation using the Markov chain Monte Carlo model[21] with baseline adjustment factors (distance control, age, refractive error, and distance PACT) and follow-up control scores was performed to impute missing control scores for each treatment group separately in the primary analysis (eAppendix in Supplement 2). Sensitivity analyses were conducted to evaluate the effects of missing data handling on study results (eAppendix in Supplement 2). The primary analysis was repeated within baseline subgroups in exploratory analyses.

Using the same ANCOVA model as the primary analysis, the mean 18-month distance control scores were compared between treatment groups. As a sensitivity analysis, the 18-month analysis was repeated, limited to 292 participants who completed the full treatment and weaning period (ie, had completed the 15-month visit) prior to early discontinuation of overminus by the data and safety monitoring committee.

Additional secondary outcomes related to the exodeviation (control and magnitude) and stereoacuity were compared between treatment groups using ANCOVA models adjusted for the baseline level of the outcome. The cumulative probabilities of deterioration by 12 and by 18 months were calculated by treatment group using Cox proportional hazards models.

As a safety outcome, mean 12-month SE cycloplegic refractive error was compared between treatment groups using ANCOVA adjusting for baseline refractive error and age. The risk ratio between treatment groups for the proportion of participants with an increase in SE myopia from baseline to 12 months of higher than 1.00 D was also calculated using the Farrington-Manning score method.[22]

Item responses for the IXT Child Symptom Survey[18] and the Parent Spectacle/Symptom Survey and median scores for the child and parent IXTQ[20] components were tabulated. The IXTQ domain scores were compared between treatment groups at 12 and 18 months using the Wilcoxon rank sum test.

We adjusted *P* values to control the false discovery rate[23] at 5% separately for IXTQ domain scores and for all other secondary outcomes (eAppendix in Supplement 2). All analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

Between January 2017 and January 2019, 386 children were enrolled at 56 sites, with 196 children assigned to overminus lens therapy and 190 children to nonoverminus lens treatment. Baseline demographic characteristics (age: mean [SD], 6.3 [2.1] years; range, 3.0-11.0 vs 3.0-10.7 years; sex: 226 [59%] female; 112 [57%] vs 114 [60%] girls) and clinical characteristics appeared similar in the treatment groups (**Table 1**).

The overall completion rate was 93% for the 12-month follow-up and 86% for the 18-month follow-up. Twelve-month follow-up was incomplete for 7 of 196 participants (4%) in the overminus group and 21 of 190 participants (11%) in the nonoverminus group (**Figure**). Eighteen-month follow-up was incomplete for 20 of 196 participants (10%) in the overminus group and 35 of 190 participants (18%) in the nonoverminus group (Figure). Of 331 participants who completed the 18-month visit, only 292 (88%) completed the full treatment and weaning protocol. Clinical characteristics of those with incomplete vs complete 18-month follow-up are provided in eTable 3 in Supplement 2. All examiners assessing outcome measures were masked to the participants' assigned treatment.

Treatment Adherence

Spectacle wear adherence was reported as excellent for 149 children in the overminus group and 144 children in the nonoverminus group, which was 76% of each treatment group, at 12 months (eTable 4 in Supplement 2). Two participants in each treatment group received nonstudy IXT treatment before 12 months.

Twelve-Month Efficacy Analyses (Primary Outcome)

The overminus group, wearing their study spectacles, had better mean (SD) distance control after 12 months of treatment (1.8 [1.3] points) compared with the nonoverminus group (2.8 [1.5] points) (adjusted treatment group difference, −0.8 points; 95% CI, −1.0 to −0.5 points; *P* < .001) (**Table 2**; eFigure 1 in Supplement 2). Mean distance control scores were imputed for 34 participants (10 in overminus and 24 in nonoverminus). Several sensitivity analyses that were completed (eAppendix in Supplement 2) yielded results similar to the primary analysis.

Treatment group differences in secondary outcomes favored the overminus group, except for little or no difference in stereoacuity (Table 2). In exploratory analyses, a 12-month treatment effect favoring the overminus group was observed across all baseline subgroups, including baseline distance con-

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Table 1. Baseline Demographic and Clinical Characteristics by Treatment Group

Characteristic	No. (%) of participants	
	Overminus	Nonoverminus
Overall	196 (100)	190 (100)
Sex		
Female	112 (57)	114 (60)
Male	84 (43)	76 (40)
Race/ethnicity		
Asian	6 (3)	10 (5)
Black/African American	34 (17)	28 (15)
Hispanic	31 (16)	40 (21)
White	113 (58)	91 (48)
Other	12 (6)	21 (11)
Age at randomization, y		
3 to <7	123 (63)	120 (63)
7 to <11	73 (37)	70 (37)
Mean (SD) [range]	6.4 (2.0) [3.0 to 11.0]	6.2 (2.2) [3.0 to 10.7]
Refractive error (spherical equivalent), D[a]		
>0.50	58 (30)[b]	59 (31)[b]
>−0.75 to 0.50	101 (52)	96 (51)
−0.75 to >−3.00	29 (15)	32 (17)
≤−3.00	8 (4)	3 (2)
Mean (SD) [range]	−0.02 (1.11) [−6.00 to 1.25]	0.01 (0.94) [−3.75 to 1.00]
Prior nonsurgical treatment of IXT		
None	126 (64)	137 (72)
Patching only	53 (27)	33 (17)
Vision therapy only	10 (5)	11 (6)
Patching plus other	4 (2)	6 (3)
Other	3 (2)	3 (2)
Randot Preschool Sterioacuity test score at near, arcseconds[c]		
40-100	120 (64)	112 (61)
200-800	52 (28)	55 (30)
Nil	16 (9)	16 (9)
Median, log (arcseconds)	2.0	2.0
Mean distance visual acuity[d]		
20/12 to 20/20	115 (59)	112 (59)
20/25 to 20/32	70 (36)	69 (36)
20/40 to 20/50	11 (6)	9 (5)
IOD of distance visual acuity, lines (logMAR)		
0	130 (66)	115 (61)
0.1	57 (29)	61 (32)
0.2	9 (5)	14 (7)
Spectacle wear		
Does not wear spectacles	140 (71)	142 (75)
Wearing spectacles for at least 1 wk	56 (29)	48 (25)
Exotropia[e]		
Control at distance		
0 to <1	NA	NA
1 to <2	NA	NA
2 to <3	84 (43)	78 (41)
3 to <4	56 (29)	52 (27)
4 to 5	56 (29)	60 (32)

(continued)

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Table 1. Baseline Demographic and Clinical Characteristics by Treatment Group (continued)

Characteristic	No. (%) of participants	
	Overminus	Nonoverminus
Mean (SD) [range]	3.2 (1.0) [2 to 5]	3.2 (1.0) [2 to 5]
Control at near		
0 to <1	37 (19)	46 (24)
1 to <2	80 (41)	65 (34)
2 to <3	39 (20)	44 (23)
3 to <4	31 (16)	27 (14)
4 to 5	9 (5)	8 (4)
Mean (SD) [range]	1.7 (1.1) [0 to 4.7]	1.6 (1.1) [0 to 4.7]
PACT exodeviation, Δ[f]		
At distance		
No exodeviation (orthophoria)	NA	NA
1-9	NA	NA
10-15	5 (3)	6 (3)
16-18	42 (21)	22 (12)
19-25	86 (44)	91 (48)
30-35	54 (28)	50 (26)
40-45	9 (5)	19 (10)
≥50	0	2 (1)
Esodeviation	NA	NA
Mean (SD) [range]	25 (7) [15 to 45]	27 (8) [15 to 50]
At near[f]		
No exodeviation (orthophoria)	2 (1)	3 (2)
1-9	27 (14)	24 (13)
10-15	45 (23)	45 (24)
16-18	36 (18)	29 (15)
19-25	57 (29)	59 (31)
30-35	24 (12)	21 (11)
40-45	4 (2)	8 (4)
≥50	1 (<1)	0
Esodeviation	0	1 (<1)
Mean (SD) [range]	18 (9) [0 to 50]	19 (10) [−4 to 45]

Abbreviations: D, diopters; IOD, interocular difference; IXT, intermittent exotropia; NA, not applicable; PACT, prism and alternate cover test; Δ, prism diopters.

[a] Spherical equivalent refractive error in more myopic eye if myopic or in less hyperopic eye if hyperopic.

[b] Two participants in the overminus group were not eligible owing to spherical equivalent refractive error in the least hyperopic eye >1.00 D, and 1 participant in the nonoverminus group was ineligible owing to prior strabismus surgery. These ineligible participants were included in the primary analysis.

[c] Log (arcseconds) stereoacuity values range from 1.6 (40 arcseconds) to 3.2 (nil); thus, lower values are better. Eight participants in the overminus group (5%) and 7 in the nonoverminus group (7%) did not understand test instructions to complete the stereotest; therefore, their stereoacuity at baseline was missing.

[d] Mean between 2 eyes.

[e] Mean of 3 assessments performed throughout the examination. Mean distance exotropia control of 2 points or higher (worse) was required for eligibility. Mean near exotropia control of lower than 5 points (ie, could not be constant on all 3 of the measures) was required for eligibility.

[f] PACT at distance was required to be at least 15Δ for eligibility. In addition, near deviation could not exceed distance deviation by more than 10Δ by PACT for eligibility (ie, convergence insufficiency type IXT was excluded). Negative values represent esodeviation.

trol, baseline SE refractive error, age, accommodative convergence to accommodation ratio, sex, and race/ethnicity (eFigure 2 in Supplement 2).

Eighteen-Month Efficacy Analyses

At the 18-month visit (3 months after overminus spectacles were discontinued), the mean distance control was 2.4 points for 176 participants in the overminus group vs 2.7 points in 155 participants in the nonoverminus group (adjusted treatment group difference, −0.2; 95% CI, −0.5 to 0.04; $P = .09$) (Table 2). Mean distance control scores were imputed for 68 participants (29 in overminus and 39 in nonoverminus). There were little or no differences between treatment groups for secondary outcomes at 18 months (Table 2).

Safety

Based on cycloplegic retinoscopy, the overminus group showed a greater SE myopic change than the nonoverminus group (−0.42 vs −0.04 D; adjusted treatment group difference, −0.37 D; 95% CI, −0.49 to −0.26 D; $P < .001$). Of 189 children in the overminus group, 33 (17%) had higher than 1.00 D of myopic shift compared with 2 of 169 children (1%) in the nonoverminus group, with a risk ratio of 14.8 (95% CI, 4.0-182.6) (**Table 3**). The increased myopic shift in the overminus vs nonoverminus groups occurred particularly in children who already had myopia compared with children with emmetropia or hyperopia at baseline (Table 3). Cycloplegic autorefraction data were available in one-third of participants and yielded results similar to the cycloplegic retinoscopy findings (Table 3). The overminus and nonoverminus groups appeared similar in development of esotropia (4 of 189 [2%] vs 4 of 169 [2%]), 2 or more line decrease in visual acuity (12 of 189 [6%] vs 10 of 169 [6%]), and amblyopia treatment prescribed by 12 months (2 of 189 [1%] vs (1 of 169 [1%]).

IXT Symptom and Spectacle Symptom Data

At 12 months, the frequency of most IXT symptoms appeared relatively similar between treatment groups, except more children in the overminus group (71 of 189 [38%]) reported that their eyes hurt sometimes or always compared with the

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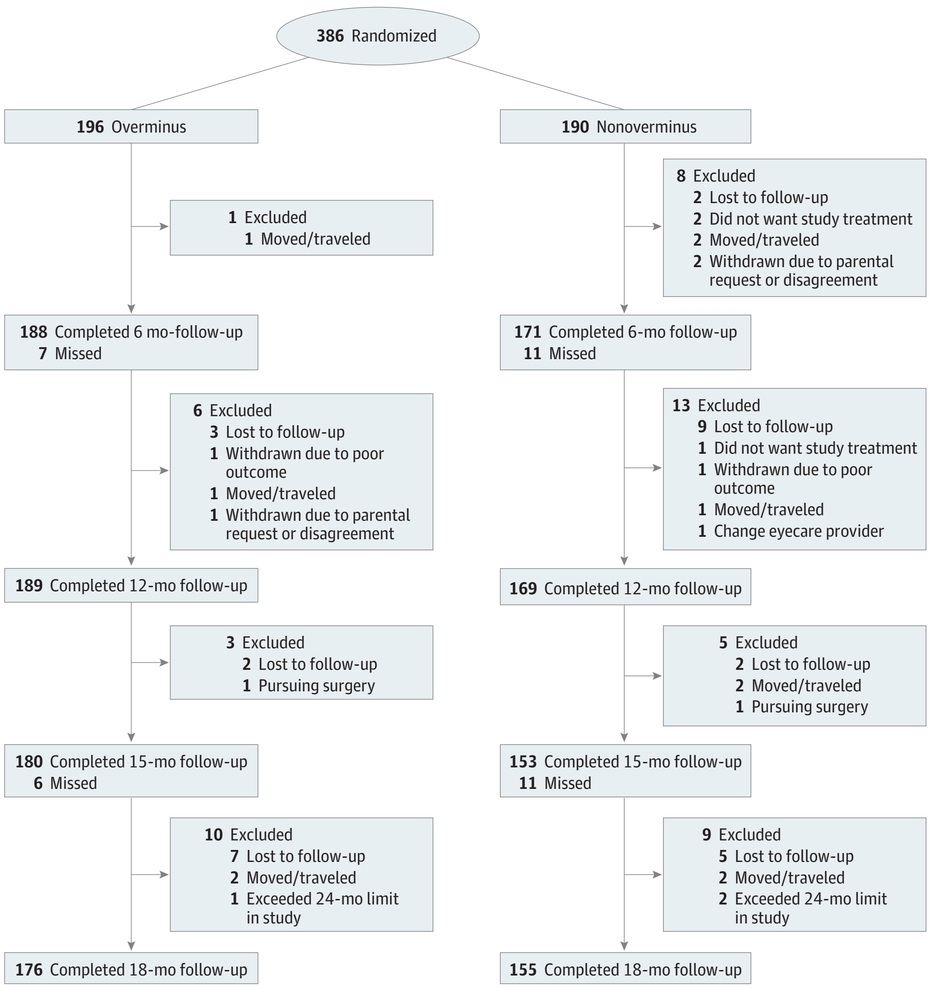
Figure. Flow of Participants Through Study



Completed represents the number of randomized participants who completed the visit. One participant in each treatment group underwent strabismus surgery, with the overminus group participant also discontinuing overminus spectacles. One participant in the nonoverminus group had vision therapy, and 1 participant in the overminus wore a different pair of spectacles at school. Two participants in the nonoverminus group started overminus spectacles after meeting stereoacuity deterioration at the 6-month visit.

nonoverminus group (37 of 169 [22%]) (eTable 5 in Supplement 2). Parent-reported symptom and spectacle data are given in eTable 6 in Supplement 2.

Health-Related Quality of Life Associated With IXT

At 12 months, health-related quality of life was scored as 78.8 (overminus) vs 71.5 (nonoverminus) on the psychosocial subscale, 75.1 (overminus) vs 70.6 (nonoverminus) on the function subscale, and 68.7 (overminus) vs 54.2 (nonoverminus) on the surgery subscale of the parent IXTQ; little or no difference was observed in the child IXTQ scores between treatment groups. At 18 months, there were no treatment group differences in the child or the parent IXTQ scores (eTable 7 in Supplement 2).

Discussion

This randomized clinical trial of 3- to 10-year-old children with IXT found that the overminus group had a better distance IXT control score while wearing overminus spectacles at 1 year after study treatment compared with the nonoverminus group, but this treatment effect did not persist after the participants were weaned off the overminus spectacles. In addition, the overminus group had a greater myopic shift at 12 months compared with the nonoverminus group, with the risk of higher than 1.00 D of myopic shift during this period being approximately 15 times that of the nonoverminus group.

Improved IXT control while wearing overminus spectables has been reported in a previous pilot randomized clinical trial,[11] 2 prospective observational studies without comparison groups,[6,9] and retrospective case series reports.[3,5] Aside from the pilot randomized clinical trial, the present trial differs from the previous studies in study design, strength of overminus power used, treatment duration, and outcome measures, making comparisons across studies difficult. The 0.8-point mean improvement in the distance IXT control score while wearing overminus spectacles at 12 months in the present study is nearly identical to the 0.75-point mean improvement found in the previous 8-week pilot randomized clinical trial that evaluated the same overminus lens power.[11] Taken together, these 2 studies suggest that there is a relatively fast response to overminus spectacles after treatment initiation, which then appears to remain stable over time, given that IXT

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Table 2. Exotropia Control and Secondary Outcomes at Follow-up (Mean of 3 Measurements)[a]

	No. (%) of participants			
	12-mo Visit (primary outcome)		18-mo Visit (secondary outcome)	
Measure	Overminus (n = 189)	Nonoverminus (n = 169)	Overminus (n = 176)	Nonoverminus (n = 155)
Distance control score (points)				
0 to <1	38 (20)	8 (5)	21 (12)	16 (10)
1 to <2	60 (32)	42 (25)	53 (30)	38 (25)
2 to <3	52 (28)	47 (28)	42 (24)	35 (23)
3 to <4	19 (10)	21 (12)	20 (11)	15 (10)
4 to 5	20 (11)	51 (30)	40 (23)	51 (33)
Mean (SD) [range]	1.8 (1.3) [0 to 5]	2.8 (1.5) [0 to 5]	2.4 (1.5) [0 to 5]	2.7 (1.6) [0 to 5]
Difference, mean (2-sided 95% CI)[b,c]	−0.8 (−1.0 to −0.5)		−0.2 (−0.5 to 0.04)	
P value for difference, mean	<.0001		.09	
Change from baseline (points)[d]				
Mean (SD) [range]	1.3 (1.4) [−2.3 to 5.0]	0.5 (1.3) [−3.0 to 4.3]	0.8 (1.5) [−3.0 to 4.7]	0.5 (1.6) [−3.0 to 4.7]
Improved ≥1 point[c,e]	116 (61)	71 (42)	86 (49)	68 (44)
Difference, % (2-sided 95% CI)	19 (7 to 29)		4 (−7 to 15)	
P value for difference	.0009		.61	
Improved ≥2 points[c,e]	65 (34)	24 (14)	48 (27)	30 (19)
Difference, % (2-sided 95% CI)	20 (10 to 28)		8 (−2 to 17)	
P value for difference	.0003		.18	
Near control score (points)				
0 to <1	96 (51)	64 (38)	72 (41)	59 (38)
1 to <2	59 (31)	55 (33)	60 (34)	46 (30)
2 to <3	21 (11)	13 (8)	16 (9)	18 (12)
3 to <4	9 (5)	17 (10)	15 (9)	16 (10)
4 to 5	4 (2)	20 (12)	13 (7)	16 (10)
Mean (SD) [range]	1.0 (1.1) [0 to 5]	1.5 (1.5) [0 to 5]	1.3 (1.3) [0 to 5]	1.5 (1.5) [0 to 5]
Difference, mean (2-sided 95% CI)[b,c]	−0.5 (−0.8 to −0.3)		−0.2 (−0.5 to 0.1)	
P value for difference, mean	<.0001		.19	
Change from baseline (points)[d]				
Mean (SD) [range]	0.7 (1.3) [−3.3 to 3.7]	0.1 (1.4) [−3.7 to 3.7]	0.4 (1.4) [−3.7 to 3.7]	0.1 (1.5) [−4.7 to 3.3]
No spontaneous tropia during control testing at distance and near[e]	115 (61)	62 (37)	85 (48)	60 (39)
Difference, % (2-sided 95% CI)[c]	24 (13 to 34)		9 (−2 to 19)	
P value for difference	.0003		.18	
Deterioration (motor or stereo) by specified time[f]	5 (1)	7 (4)	6 (2)	16 (7)
Randot Preschool Stereoacuity test score, arcseconds[g]				
40-60	101 (56)	99 (61)	114 (67)	97 (65)
100-400	66 (36)	51 (31)	44 (26)	40 (27)
800 or Nil	14 (8)	12 (7)	12 (7)	12 (8)
Median, log (arcseconds)	1.8	1.8	1.8	1.8
Mean (SD), log (arcseconds)[h]	2.0 (0.4)	2.0 (0.4)	1.9 (0.4)	1.9 (0.4)
Range, log (arcseconds)	1.6 to 3.2	1.6 to 3.2	1.6 to 3.2	1.6 to 3.2
Difference, mean (95% CI)[c,i]	0.03 (−0.04 to 0.10)		−0.01 (−0.09 to 0.06)	
P value for difference	.47		.82	
Change from baseline, log (arcseconds)[j]				
Mean (SD) [range], log (arcseconds)	−0.1 (0.4) [−1.4 to 0.9]	−0.2 (0.4) [−1.4 to 0.6]	−0.2 (0.4) [−1.6 to 1.4]	−0.2 (0.4) [−1.6 to 1.2]
PACT exodeviation, Δ				
At distance				
No exodeviation (orthophoria)	2 (1)	1 (<1)	1 (<1)	0 (0)
1-9	17 (9)	3 (2)	5 (3)	3 (2)
10-15	30 (16)	9 (5)	20 (11)	10 (6)
16-18	38 (20)	22 (13)	28 (16)	23 (15)
19-25	73 (39)	73 (43)	71 (40)	64 (41)
30-35	25 (13)	52 (31)	39 (22)	40 (26)

(continued)

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Table 2. Exotropia Control and Secondary Outcomes at Follow-up (Mean of 3 Measurements)[a] (continued)

Measure	No. (%) of participants			
	12-mo Visit (primary outcome)		18-mo Visit (secondary outcome)	
	Overminus (n = 189)	Nonoverminus (n = 169)	Overminus (n = 176)	Nonoverminus (n = 155)
40-45	3 (2)	8 (5)	10 (6)	11 (7)
≥50	0 (0)	1 (<1)	1 (<1)	1 (<1)
Esodeviation	1 (<1)	0 (0)	1 (<1)	3(2)
Mean (SD) [range]	20.0 (9.0) [−2 to 45]	25.0 (8.0) [0 to 55]	23.0 (9.0) [−12 to 50]	24.0 (11.0) [−30 to 80]
Difference, mean (95% CI)[c,i]	−4.2 (−5.7 to −2.6)		0.2 (−1.8 to 2.2)	
P value for difference	<.001		.87	
Change from baseline (Δ)[j]				
Mean (SD) [range]	−5.0 (7.0) [−33 to 10]	−2.0 (8.0) [−40 to 15]	−1.0 (8.0) [−35 to 20]	−2.0 (8.0) [−36 to 40]
At near				
No exodeviation (orthophoria)	9 (5)	3 (2)	6 (3)	6 (4)
1-9	41 (22)	31 (18)	20 (11)	20 (13)
10-15	53 (28)	27 (16)	50 (28)	32 (21)
16-18	28 (15)	30 (18)	24 (14)	26 (17)
19-25	34 (18)	50 (30)	46 (26)	42 (27)
30-35	19 (10)	18 (11)	23 (13)	22 (14)
40-45	3 (2)	7 (4)	4 (2)	4 (3)
≥50	0 (0)	2 (1)	2 (1)	2 (1)
Esodeviation	2 (1)	1 (<1)	1 (<1)	1 (<1)
Mean (SD) [range]	15.0 (9.0) [−8 to 45]	18.0 (10.0) [−5 to 55]	18.0 (10.0) [−12 to 60]	19.0 (11.0) [−30 to 55]
Difference, mean (95% CI)[c,i]	−3.8 (−5.5 to −2.1)		−0.7 (−2.7 to 1.4)	
P value for difference	<.001		.61	
Change from baseline (Δ)[j]				
Mean (SD) [range]	−4.0 (8.0) [−33 to 16]	0.0 (9.0) [−27 to 30]	0.0 (10.0) [−27 to 40]	1.0 (9.0) [−27 to 30]

Abbreviations: PACT, prism and alternate cover test; Δ, prism diopters.

[a] Study spectacles were used for outcome testing for 171 participants (90%) in the overminus group and 155 participants (92%) in the nonoverminus group at the 12-month visit and for 157 participants (89%) in the overminus group and 145 participants (94%) in the nonoverminus group at the 18-month visit. Trial frames were used for all other participants.

[b] Difference in mean distance or near control (overminus − nonoverminus) and 95% CIs are from analysis of covariance model, adjusting for baseline distance or near control (respectively), age, spherical equivalent refractive error, and PACT at distance or near.

[c] Three participants (1 in overminus and 2 in nonoverminus groups) at 12 months, and 3 participants (2 in overminus and 1 in nonoverminus groups) at 18 months were excluded from this analysis owing to visits outside the analysis window.

[d] Change is calculated as baseline minus 12 months or minus 18 months; thus, a positive change represents improvement.

[e] Treatment groups were compared using a 2-sided Barnard test.

[f] Definition of deterioration available in eTable 2 in Supplement 2. Percentages shown in table are cumulative probabilities derived from Cox proportional hazards models. At 12 months, the cumulative probabilities were both less than 5%; thus, the groups were not statistically compared. At 18 months, *P* = .07 for the treatment group difference (derived from the *z* test).

[g] Stereoacuity was missing for 8 participants (4%) in the overminus and 7 participants (4%) in the nonoverminus group at 12 months and for 6 participants (3%) in the overminus group and 6 participants (4%) in the nonoverminus group at 18 months because they did not understand the test.

[h] The log (arcseconds) stereoacuity values range from 1.6 log (arcseconds) (40 arcseconds) to 3.2 (nil); thus, lower values are better.

[i] Difference in means (overminus − nonoverminus), 95% CIs, and *P* values were from analysis of covariance models adjusted for the baseline value of the measure.

[j] Change is calculated as the follow-up visit minus baseline; thus, a negative change represents improvement.

control was essentially the same at 8 weeks, 6 months, and 12 months. Exploratory analyses found a 12-month treatment benefit of overminus lens therapy across age, refractive error, distance IXT control, and the ratio of accommodative convergence to accommodation.

In the present study, the treatment benefit observed at 12 months did not persist after the participants were weaned off their overminus lenses. Two retrospective studies[5,6] have reported differing success rates of improved control after discontinuation of overminus spectacle therapy; however, neither study had a control group. In the present study, a modest improvement in distance control occurred from baseline to 18 months in both treatment groups, indicating the importance of a control group to differentiate whether the improved control was due to overminus treatment or to other factors, such as spontaneous improvement unrelated to the overminus lens treatment or regression to the mean. In clinical practice, overminus lenses are typically weaned over an extended period, either by gradually reducing the overminus lens power[5,6] (eg, 0.50-D steps)[6] or wear time,[24] given satisfactory control with the reduced overminus lens power in a clinical examination. In the present study, a 50% reduction in overminus lens power was prescribed for only 3 months, after which the lenses were discontinued regardless of exotropia control. In contrast to a more gradual and dynamic weaning procedure, the present study used a standardized, fixed overminus lens reduction of short duration that did not require numerous control assessments to improve feasibility for a multicenter clinical trial.

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Table 3. Refractive Error Change Between Baseline and 12 Months

Measure	Completing 12 mo, No. (%)	Change in spherical equivalent refractive error from baseline to 12 mo, mean (SD) D[a,b]		>1 D of spherical equivalent myopic change from baseline to 12 mo, No. (%)		>1 D of spherical equivalent myopic change from baseline to 12 mo in overminus vs nonoverminus groups, risk ratio (95% CI)[c]
		Overminus	Nonoverminus	Overminus	Nonoverminus	
No.		189	169	189	169	
Overall by cycloplegic refraction	358 (100)	−0.42 (0.69)	−0.04 (0.46)	33 (17)	2 (1)	14.8 (4.0 to 182.6)
Baseline spherical equivalent refractive error[d]						
Myopia						
No.		43	44	43	44	
−0.50 to −6.00 D	87 (100)	−1.07 (0.76)	−0.16 (0.57)	22 (51)	1 (2)	22.5 (4.1 to 667.6)
Emmetropia						
No.		60	48	60	48	
−0.375 to 0.375 D	108 (100)	−0.30 (0.64)	−0.01 (0.41)	8 (13)	1 (2)	6.4 (1.0 to 164.9)
Hyperopia						
No.		84	77	84	77	
0.50 to 1.00 D	161 (100)	−0.18 (0.44)	0.00 (0.41)	3 (4)	0	NA[e]
Overall						
No.		65	61	65	61	
By cycloplegic autorefraction[f]	126 (100)	−0.45 (0.69)	−0.05 (0.66)	12 (18)	3 (5)	3.8 (1.1 to 28.3)

Abbreviations: D, diopters; NA, not applicable.

[a] Overall treatment group difference of 12-month refractive error (overminus − nonoverminus) equal to −0.37 D (95% CI, −0.49 to −0.26 D). The difference is obtained from an analysis of covariance model adjusted for baseline spherical equivalent refractive error in the most myopic eye and age. $P < .001$ for treatment group difference. Three children were excluded from analysis owing to visits out of the analysis window.

[b] Refractive error in most myopic eye at baseline.

[c] Exact risk ratio and CIs were obtained from a Farrington-Manning score test and reflect the relative probability of a participant in the overminus group having more than 1.00 D of myopic change at 12 months compared with a participant in the nonoverminus group.

[d] Subgroups do not include 2 ineligible participants who had a refractive error greater than 1.00 D at baseline (1 with 1.125 D, and 1 with 1.25 D).

[e] Among participants who were in the hyperopic group at baseline, 3 participants in the overminus group and 0 participants in the nonoverminus group had myopic shift of more than 1.00 D at 12 months. A risk ratio could not be calculated owing to the denominator of 0.

[f] Overall treatment group difference of 12-month refractive error from cycloplegic autorefraction (overminus − nonoverminus) equal to −0.39 D (95% CI, −0.64 to −0.15 D). Difference obtained from an analysis of covariance model adjusted for baseline refractive error in the most myopic eye and age. *P* value not reported. One participant with autorefraction was excluded from analysis because the visit was outside the analysis window.

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A different weaning method may have facilitated retention of the treatment effect observed at 12 months.

Previous retrospective studies[5,25-27] that evaluated refractive error changes with overminus spectacles concluded that overminus spectacle therapy was associated with no more myopic shift than what would normally be expected for the age group being treated. In the present study, we found a greater myopic shift associated with overminus lens treatment, particularly in children with myopia already present at baseline. The treatment group difference in myopic change found in the present study supports the suggestion that the overminus lens treatment was causative. The increased risk of myopic shift should be weighed against the potential benefits of overminus spectacles when discussing this treatment with parents.

Limitations

This study has limitations. Although the 12-month follow-up completion rate was 93%, 3 times as many participants were lost to follow-up in the nonoverminus (21 [11%]) vs the overminus group (7 [4%]). This differential loss to follow-up was accounted for in the primary analysis by imputing missing 12-month data separately for each treatment group. Only 292 of 331 participants (88%) with 18-month data had completed the full treatment and weaning protocol; however, a sensitivity analysis limited to these participants yielded similar results. Another limitation is that refractive error was assessed with cycloplegic retinoscopy by an unmasked examiner, and cycloplegic autorefraction data were available for only 33% of participants. At present, it is unknown whether the myopic shift is permanent or temporary. We are collecting data on change in refractive error and axial length at 24 and 36 months in the extension phase of the present study.

Conclusions

In conclusion, after 12 months of overminus lens wear, children 3 to 10 years of age showed improved distance IXT control when assessed with their overminus spectacles; however, the treatment was associated with an increased risk of myopic shift. Because the beneficial treatment effect did not persist after the participants were weaned off overminus spectacles for 3 months and examined 3 months later, the utility of using our overminus lens treatment protocol as a primary therapy for IXT may be limited. When considering overminus lenses as a potential treatment to temporarily improve IXT control, clinicians and parents should weigh the potential benefit of better eye alignment against the increased risk of myopic shift, particularly in children who already have myopia.

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IXT5 Extension – Refractive Error Change and Overminus Lens Therapy for Childhood Intermittent Exotropia.

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Refractive Error Change and Overminus Lens Therapy for Childhood Intermittent Exotropia

Writing Committee for the Pediatric Eye Disease Investigator Group;
for the Pediatric Eye Disease Investigator Group

Visual Abstract

Supplemental content

IMPORTANCE Increased myopic shift was found to be associated with 1 year of overminus spectacle treatment for children with intermittent exotropia (IXT). Persistence of myopic shift after discontinuing overminus spectacles is unknown.

OBJECTIVE To compare refractive error change over 3 years in children with IXT originally treated with overminus vs nonoverminus spectacles.

DESIGN, SETTING, AND PARTICIPANTS This study was an 18-month extension of the Trial of Overminus Spectacle Therapy for Intermittent Exotropia cohort, which previously randomized children aged 3 to 10 years with IXT and baseline spherical equivalent refractive error (SER) between −6.00 diopters (D) and 1.00 D to overminus spectacles (−2.50 D for 12 months, −1.25 D for 3 months, and nonoverminus for 3 months) or nonoverminus spectacles. Children were recruited from 56 sites from July 2010 to February 2022. Data were analyzed from February 2022 to January 2024.

INTERVENTIONS After trial completion at 18 months, participants were followed up at 24 and 36 months. Treatment was at investigator discretion from 18 to 36 months.

MAIN OUTCOMES AND MEASURES Change in SER (cycloplegic retinoscopy) from baseline to 36 months.

RESULTS Of 386 children in the Trial of Overminus Spectacle Therapy for Intermittent Exotropia, 223 (57.8%) consented to 18 months of additional follow-up, including 124 of 196 (63.3%) in the overminus treatment group and 99 of 190 (52.1%) in the nonoverminus treatment group. Of 205 children who completed 36-month follow-up, 116 (56.6%) were female, and the mean (SD) age at randomization was 6.2 (2.1) years. Mean (SD) SER change from baseline to 36 months was greater in the overminus group (−0.74 [1.00] D) compared with the nonoverminus group (−0.44 [0.85] D; adjusted difference, −0.36 D; 95% CI, −0.59 to −0.12; *P* = .003), with 30 of 112 (26.8%) in the overminus group having more than 1 D of myopic shift compared with 14 of 91 (15%) in the nonoverminus group (risk ratio, 1.8; 95% CI, 1.0-3.0). From 12 to 36 months, mean (SD) myopic shift was −0.34 (0.67) D and −0.36 (0.66) D in the overminus and nonoverminus groups, respectively (adjusted difference, −0.001 D; 95% CI, −0.18 to 0.18; *P* = .99).

CONCLUSIONS AND RELEVANCE The greater myopic shift observed after 1 year of −2.50-D overminus lens treatment remained at 3 years. Both groups had similar myopic shift during the 2-year period after treatment weaning and cessation. The risk of myopic shift should be discussed with parents when considering overminus lens treatment.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02807350

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Intermittent exotropia (IXT) is the most common form of divergent strabismus in childhood.[1-5] Overminus lens therapy, consisting of spectacles with more minus power than cycloplegic refractive error, is a nonsurgical treatment option for childhood IXT. Clinicians classically use overminus lenses to temporarily improve IXT control in young children before considering strabismus surgery[6-11] or vision therapy or orthoptics.[7,10] If a child's IXT is well controlled while wearing the overminus spectacles, some clinicians gradually wean patients off treatment by reducing the power or wear time[8,9] to determine if the child can maintain good control without the need for further treatment.

In our previously reported randomized clinical trial (RCT) comparing overminus vs nonoverminus spectacles in children with IXT aged 3 to 10 years, the Trial of Overminus Spectacle Therapy for Intermittent Exotropia, we found improved distance IXT control after 12 months of overminus (−2.50 diopters [D]) spectacles. The treatment effect did not persist after participants were weaned off overminus spectacles for 3 months and examined 3 months later.[12] Importantly, we also found the treatment was associated with increased myopic shift over 12 months,[12] particularly among children with myopia at baseline. The primary objective of the current extension study was to evaluate change in refractive error 2 years after weaning and treatment discontinuation had begun to determine whether the myopic shift seen at 12 months persisted 3 years from treatment initiation.

Key Points

Question In children with intermittent exotropia, did the greater myopic shift observed after 1 year of overminus lens treatment (compared with nonoverminus treatment) persist 2 years after the start of weaning and cessation?

Findings In this extension of the Trial of Overminus Spectacle Therapy for Intermittent Exotropia, mean myopic shift from baseline to 3 years was greater in the overminus group compared with the nonoverminus group. The myopic shift was similar between treatment groups from 1 year to 3 years.

Meaning The myopic shift associated with 1 year of −2.50-diopter overminus lens treatment persisted after discontinuing the overminus spectacles, but it did not increase further compared with the nonoverminus group after overminus lens treatment weaning and cessation.

Methods

The study was funded by the National Eye Institute of the National Institutes of Health and conducted according to the Declaration of Helsinki tenets by the Pediatric Eye Disease Investigator Group at 56 academic and community-based clinical sites. Community-based sites were approved by the Jaeb Center for Health Research Institutional Review Board. Institutional review boards for each site approved the protocol and Health Insurance Portability and Accountability Act (HIPAA)-compliant informed consent forms. Each participant's parent or guardian gave written informed consent, and if required, each participant gave assent. Study participants received $50 compensation per visit. The study is registered online[13]; the trial protocol can be found in Supplement 1, and the statistical analysis plan can be found in Supplement 2. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

18-Month Randomized Trial

The initial 18-month RCT[12] included 386 children aged 3 to 10 years with spherical equivalent refractive error (SER) between −6.00 D and 1.00 D as well as IXT of 15 prism diopters (Δ) or more with a distance IXT control score (mean of 3 measures) of 2 points or more (range from 0 [phoria] to 5 [constant]).[14,15] Participants were randomly assigned to overminus spectacles (−2.50 D over cycloplegic refraction for 12 months, −1.25 D for 3 months, then nonoverminus for 3 months; n = 189) or nonoverminus spectacles (n = 169) for 18 months, to be worn full-time.[12] As a safety outcome, cycloplegic refraction was performed at baseline and 12 months to monitor change. Two years and 10 months after the RCT began, the data and safety monitoring committee observed greater myopic shift in the overminus group and recommended discontinuation of overminus spectacles for those still wearing the spectacles (17 of 196 [8.7%]) and adding a cycloplegic refraction at the 18-month visit for the remaining participants. Additional details have been published.[12] Self-reported race and ethnicity data were collected via a questionnaire; categories included American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, more than 1 race, Native Hawaiian or Other Pacific Islander, White, and unknown or not reported.

Post-RCT Follow-Up (Extension Study)

In December 2019, when 250 of 386 participants (64.8%) had completed the 18-month RCT, participants were asked to participate in the present post-RCT extension study. Follow-up visits occurred at 24 months (range, 21 to 27 months) and 36 months (range, 33 to 39 months) from randomization. A masked examiner measured near stereoacuity and performed 3 IXT control assessments (beginning, middle, and end of examination), cover-uncover test, and prism and alternate cover test at distance and near. Cycloplegic retinoscopy was performed 30 to 45 minutes following at least 1 drop of cyclopentolate, 1%. Cycloplegic autorefraction, axial length, flat corneal curvature, anterior chamber depth, and lens thickness were measured if autorefractors and biometers were available at the site. Treatment of IXT from 18 to 36 months was at investigator discretion.

Statistical Analysis

The primary analyses compared mean SER change by retinoscopy (more myopic eye at baseline) from baseline to 24 months and baseline to 36 months using analysis of covariance with adjustment for baseline SER in all participants who completed the respective visit. Missing data were not imputed and no adjustment for multiplicity was made for these primary outcomes because they were safety analyses.

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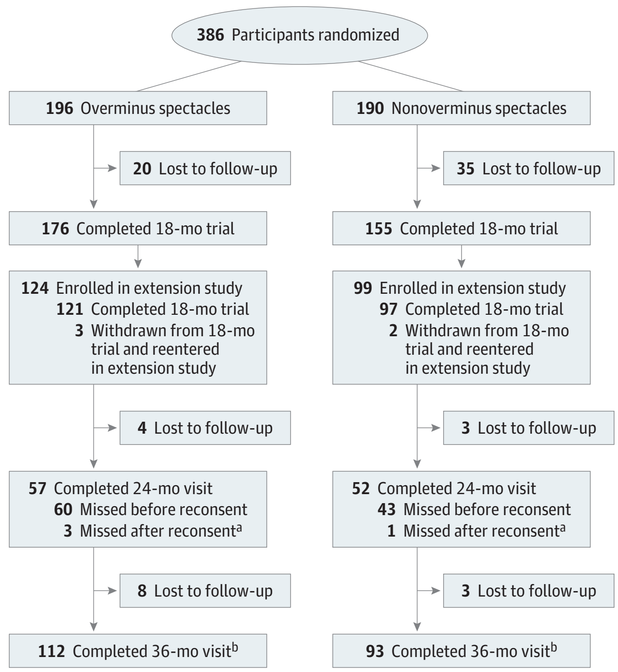
As sensitivity analyses, the primary analyses were repeated but limited to participants who (1) completed the 24-month and 36-month visits within the study visit window, (2) were not treatment crossovers during the RCT, and (3) completed the 12-month RCT primary outcome visit. A fourth sensitivity analysis using the last-observation-carried-forward method imputed the last SER recorded for participants who started orthokeratology treatment. A fifth sensitivity analysis used multiple imputation to impute the missing 24-month and 36-month SER data for participants in the extension study.

A secondary outcome was the proportion of participants with an increase in SER myopia more than 1.00 D from baseline to 24 and 36 months, both overall and by baseline SER subgroups (−0.50 to −6.00 D, −0.375 to 0.375 D, and 0.50 to 1.00 D). The risk ratio (RR) between treatment groups for this proportion and the associated 95% CIs were calculated at both time points using Poisson regression with robust error variance and adjustment for baseline SER.[16] As a sensitivity analysis for the myopia subgroup, the RR was also calculated for a different baseline refractive error subgroup (myopia: less than 0 to −6.00 D). Exploratory analyses on the SER outcomes were repeated based on cycloplegic autorefraction data (from participants with available data).

A post hoc treatment group comparison of mean SER change from 12 months (ie, time of tapering to −1.25 D overminus followed by discontinuing overminus at 15 months) to 36 months used methods similar to the primary analysis. In addition, mean change in SER from baseline to 12 months, 12 to 24 months, and 24 to 36 months were tabulated by treatment group.

As secondary analyses, axial length, flat corneal curvature, anterior chamber depth, and lens thickness of the most myopic eye at baseline were compared between treatment groups at 24 and 36 months using an analysis of variance model. Adjusting for baseline values was not possible because these measures were not collected at baseline. *P* values and 95% CIs were adjusted using the 2-stage step-up procedure to control the false discovery rate[17] at 5%. Significance was set at $P < .05$, and all *P* values were 2-tailed. In exploratory analyses, the differences between treatment groups in exodeviation control, exodeviation magnitude, and near stereoacuity were estimated using analysis of covariance adjusted for the baseline measures; because of the exploratory nature of the analyses, only 95% CIs and not *P* values are reported. All analyses were conducted using SAS version 9.4 (SAS Institute).

Figure 1. Study Flowchart



[a] Seven in the overminus group and 4 in the nonoverminus group completed the 24-month visit out of the analysis window (≥630 and ≤899 days from randomization) for the primary analysis.

[b] One in the overminus group and 3 in the nonoverminus group completed the 30-month visit out of the analysis window (≥900 and ≤1440 days from randomization) for the primary analysis.

Results

Of 386 children in the Trial of Overminus Spectacle Therapy for Intermittent Exotropia, 223 (57.8%) consented to 18 months of additional follow-up, including 124 of 196 (63.3%) in the overminus treatment group and 99 of 190 (52.1%) in the nonoverminus treatment group (**Figure 1**). Because 103 of 223 participants (46.2%) were at least 30 months postrandomization at the time of consent, a 24-month visit was not possible, which contributed to only 57 of 196 (29.1%) in the overminus group and 52 of 190 (27.4%) in the nonoverminus group completing this visit. The 36-month visit was completed by 112 of 196 participants (57.1%) and 93 of 190 participants (48.9%), respectively; of these, 116 (56.6%) were female, and the mean (SD) age at randomization was 6.2 (2.1) years. Baseline demographic and clinical characteristics, SER change from baseline to 12 months, and distance IXT control at 12 and 18 months appeared similar between participants who did and did not complete the 36-month visit (**Table 1**).

SER (Primary Outcomes)

Overall, the overminus group showed a greater mean (SD) SER myopic shift from baseline than the nonoverminus group at both 24 months (−0.61 [0.94] D vs −0.14 [0.65] D; adjusted difference, −0.52 D; 95% CI, −0.79 to −0.24; $P < .001$) and 36 months (−0.74 [1.00] D vs −0.44 [0.85] D; adjusted difference, −0.36 D; 95% CI, −0.59 to −0.12; $P = .003$) (**Table 2**). Sensitivity analyses yielded similar results (eTable 2 in Supplement 3).

At 24 months, 14 of 57 overminus participants (25%) had more than 1.00 D of myopic shift compared with 4 of 52 (8%) assigned to nonoverminus treatment (adjusted RR, 3.9; 95% CI, 1.6-9.3; $P = .002$). At 36 months, 30 of 112 (26.8%) in the overminus group had more than 1.00 D of myopic shift compared with 14 of 91 (15%) in the nonoverminus group

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Table 1. Participant and Ocular Characteristics by 36-Month Visit Completion Status

Characteristic	No. (%)			
	Completed 36-mo follow-up		Did not complete 36-mo follow-up	
	Overminus (n = 112)	Nonoverminus (n = 93)	Overminus (n = 84)	Nonoverminus (n = 97)
Sex				
Female	64 (57)	52 (56)	48 (57)	62 (64)
Male	48 (43)	41 (44)	36 (43)	35 (36)
Race and ethnicity[a]				
Asian	3 (3)	5 (5)	3 (4)	5 (5)
Black or African American	19 (17)	12 (13)	15 (18)	16 (16)
Hispanic or Latino	21 (19)	22 (24)	10 (12)	18 (19)
White	60 (54)	46 (49)	53 (63)	45 (46)
Other race	9 (8)	8 (9)	3 (4)	13 (13)
Age at randomization, y				
3-<7	68 (61)	65 (70)	55 (65)	55 (57)
7-<11	44 (39)	28 (30)	29 (35)	42 (43)
Mean (SD; range)	6.4 (2.1; 3.0 to 11.0)	6.0 (2.1; 3.0 to 10.7)	6.4 (2.0; 3.0 to 11.0)	6.5 (2.2; 3.1 to 10.7)
SER, D[b]				
>0.50	30 (27)	24 (26)	28 (33)	35 (36)
>−0.75 to 0.50	65 (58)	47 (51)	36 (43)	49 (51)
−0.75 to >−3.00	12 (11)	20 (22)	17 (20)	12 (12)
≤−3.00	5 (4)	2 (2)	3 (4)	1 (1)
Mean (SD; range)	0.01 (1.11; −6.00 to 1.25)	−0.11 (1.05; −3.75 to 1.00)	−0.05 (1.12; −3.75 to 1.00)	0.13 (0.80; −3.25 to 1.00)
Change in SER from baseline to 12 mo, D				
Mean (SD; range)	−0.40 (0.66; −2.50 to 1.50)	−0.08 (0.46; −1.50 to 1.50)	−0.45 (0.72; −2.25 to 0.75)	0 (0.45; −1.00 to 1.00)
Prior nonsurgical treatment for IXT				
None	73 (65)	67 (72)	53 (63)	70 (72)
Patching only	26 (23)	17 (18)	27 (32)	16 (16)
Vision therapy only	7 (6)	5 (5)	3 (4)	6 (6)
Patching plus other treatment	3 (3)	4 (4)	1 (1)	2 (2)
Other treatment	3 (3)	0	0	3 (3)
Randot preschool stereoacuity at near, arcseconds[c]				
40 to 100	69 (64)	56 (63)	51 (64)	56 (60)
200 to 800	30 (28)	28 (31)	22 (28)	27 (29)
Nil	9 (8)	5 (6)	7 (9)	11 (12)
Median, log(arcseconds)	2.0	2.0	2.0	2.0
Mean distance visual acuity, Snellen equivalents[d]				
20/12 to 20/20	57 (51)	33 (35)	29 (35)	49 (51)
20/25 to 20/32	46 (41)	52 (56)	49 (58)	42 (43)
20/40 to 20/50	9 (8)	8 (9)	6 (7)	6 (6)
IOD of distance visual acuity, logMAR				
0	85 (76)	53 (57)	45 (54)	62 (64)
0.1	22 (20)	31 (33)	35 (42)	30 (31)
0.2	5 (4)	9 (10)	4 (5)	5 (5)
Prior spectacle wear				
No	79 (71)	65 (70)	61 (73)	77 (79)
Yes	33 (29)	28 (30)	23 (27)	20 (21)
Exotropia control at distance[e]				
2 to <3	51 (46)	41 (44)	33 (39)	37 (38)
3 to <4	34 (30)	22 (24)	22 (26)	30 (31)
4 to 5	27 (24)	30 (32)	29 (35)	30 (31)
Mean (SD; range)	3.1 (1.0; 2.0 to 5.0)	3.2 (1.1; 2.0 to 5.0)	3.3 (1.1; 2.0 to 5.0)	3.3 (1.0; 2.0 to 5.0)

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Table 1. Participant and Ocular Characteristics by 36-Month Visit Completion Status (continued)

Characteristic	No. (%) Completed 36-mo follow-up: Overminus (n = 112)	Completed 36-mo follow-up: Nonoverminus (n = 93)	Did not complete 36-mo follow-up: Overminus (n = 84)	Did not complete 36-mo follow-up: Nonoverminus (n = 97)
Change in exotropia control at distance from baseline to 12 mo, mean (SD; range)[e]	1.3 (1.4; −2.3 to 5.0)	0.4 (1.2; −3.0 to 3.0)	1.4 (1.3; −1.0 to 5.0)	0.7 (1.5; −2.3 to 4.3)
Change in exotropia control at distance from baseline to 18 mo, mean (SD; range)[e]	0.8 (1.4; −2.3 to 4.3)	0.3 (1.5; −3.0 to 4.7)	0.9 (1.5; −3.0 to 4.7)	0.8 (1.7; −3.0 to 4.7)
Exotropia control at near[e]				
0 to <1	25 (22)	31 (33)	12 (14)	15 (15)
1 to <2	37 (33)	32 (34)	43 (51)	33 (34)
2 to <3	30 (27)	15 (16)	9 (11)	29 (30)
3 to <4	16 (14)	13 (14)	15 (18)	14 (14)
4 to 5	4 (4)	2 (2)	5 (6)	6 (6)
Mean (SD; range)	1.7 (1.1; 0 to 4.7)	1.4 (1.1; 0 to 4.3)	1.7 (1.2; 0 to 4.7)	1.9 (1.1; 0 to 4.7)
PACT exodeviation at distance, Δ[f]				
10-15	4 (4)	2 (2)	1 (1)	4 (4)
16-18	27 (24)	12 (13)	15 (18)	10 (10)
19-25	49 (44)	44 (47)	37 (44)	47 (48)
30-35	26 (23)	22 (24)	28 (33)	28 (29)
40-45	6 (5)	12 (13)	3 (4)	7 (7)
≥50	0	1 (1)	0	1 (1)
Esodeviation	0	0	0	0
Mean (SD; range)	24 (7; 15 to 45)	27 (8; 15 to 50)	25 (6; 15 to 40)	26 (7; 15 to 50)
PACT exodeviation at near, Δ[f]				
No exodeviation (orthophoria)	1 (<1)	1 (1)	1 (1)	2 (2)
1-9	16 (14)	10 (11)	11 (13)	14 (14)
10-15	23 (21)	21 (23)	22 (26)	24 (25)
16-18	27 (24)	15 (16)	9 (11)	14 (14)
19-25	30 (27)	30 (32)	27 (32)	29 (30)
30-35	12 (11)	10 (11)	12 (14)	11 (11)
40-45	3 (3)	6 (6)	1 (1)	2 (2)
≥50	0	0	1 (1)	0
Esodeviation	0	0	0	1 (1)
Mean (SD; range)	18 (9; 0 to 45)	20 (10; 0 to 45)	19 (9; 0 to 50)	17 (9; −4 to 45)

Abbreviations: Δ, prism diopter; D, diopters; IOD, interocular difference; IXT, intermittent exotropia; PACT, prism and alternate cover test; SER, spherical equivalent refractive error.

[a] Race and ethnicity data were self-reported. The other race category includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple, and unknown or unreported race.

[b] SER in the most myopic eye.

[c] Log(arcseconds) stereoacuity values range from 1.6 (40 arcseconds) to 3.2 (nil), with lower values being better. Four participants in the overminus group and 3 in the nonoverminus group who did not enroll in the extension study as well as 4 participants each in the overminus group and nonoverminus groups who enrolled in the extension study did not understand test instruction to complete the stereo test; therefore, their stereoacuity at baseline was missing.

[d] Mean of the participant's 2 eyes.

[e] Mean of 3 assessments performed throughout the examination. Mean distance exotropia control of 2 points or higher (ie, worse) was required for eligibility. Change in distance exotropia control was calculated as baseline minus follow-up values, so positive change indicates improvement. Mean near exotropia control of less than 5 points (ie, could not be constant on all 3 of the measures) was required for eligibility.

[f] PACT at distance was required to be at least 15 Δ for eligibility. Additionally, the near exodeviation could not exceed that at distance by more than 10 Δ (by PACT) for eligibility (ie, convergence insufficiency type IXT was excluded). Negative values represent esodeviation.

(adjusted RR, 1.8; 95% CI, 1.0-3.0; $P = .045$) (Table 2). Based on baseline SER subgroups, RRs for developing more than 1.00 D myopic shift over 3 years between the overminus and nonoverminus groups were 2.6 (95% CI, 1.3-5.1) for participants with baseline SER of −0.50 to −6.00 D, 2.5 (95% CI, 0.8-7.6) for those with baseline SER of −0.375 to 0.375 D, and 0.7 (95% CI, 0.2-3.4) for those with baseline SER 0.50 to 1.00 D (Table 2). The RR was 1.8 (95% CI, 1.0-3.2) in the sensitivity analysis using baseline myopia defined −6.00 D or less.

Between 12 and 36 months, there was no difference in mean (SD) myopic shift between the overminus and nonoverminus groups (−0.34 [0.67] D in the overminus group and −0.36 [0.66] D in the nonoverminus group; adjusted difference, −0.001 D; 95% CI, −0.18 to 0.18; $P = .99$). The mean (SD) myopic shift was −0.20 (0.55) D in the overminus group and −0.07 (0.45) D in the nonoverminus group from 12 to 24 months and −0.08 (0.41) D and −0.26 (0.44) D, respectively, from 24 to 36 months (Table 2). Mean SER change between baseline and

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Table 2. Refractive Error During Follow-Up in the Most Myopic Eye at Baseline

Measure	Overall (cycloplegic refraction)	Baseline SER (cycloplegic refraction)[a]			Overall (cycloplegic autorefraction)[b]
		−0.50 D to −6.00 D	−0.375 D to 0.375 D	0.50 D to 1.00 D	
12 mo					
SER at 12 mo					
Overminus group					
Total, No.	189	43	60	84	103
Mean (SD)	−0.45 (1.55)	−2.79 (1.38)	−0.23 (0.67)	0.54 (0.45)	−0.23 (1.63)
Nonoverminus group					
Total, No.	169	44	48	77	104
Mean (SD)	−0.04 (1.17)	−1.51 (1.22)	0.05 (0.47)	0.74 (0.44)	0.15 (1.20)
Change in SER from baseline to 12 mo					
Overminus group					
Total, No.	189	43	60	84	65
Mean (SD)	−0.42 (0.69)	−1.07 (0.76)	−0.30 (0.64)	−0.18 (0.44)	−0.45 (0.69)
Nonoverminus group					
Total, No.	169	44	48	77	61
Mean (SD)	−0.04 (0.46)	−0.16 (0.57)	−0.01 (0.41)	0 (0.41)	−0.05 (0.66)
>1.00 D of SER myopic change from baseline to 12 mo, No./total No. (%)					
Overminus group	33/189 (17)	22/43 (51)	8/60 (13)	3/84 (4)	12/65 (18)
Nonoverminus group	2/169 (1)	1/44 (2)	1/48 (2)	0/77	3/61 (5)
RR (95% CI)[c]	13.3 (3.3-53.5)	21.3 (2.9-157.9)	6.5 (0.9-48.5)	NA[d]	4.3 (1.1-16.3)
24 mo					
SER at 24 mo					
Overminus group					
Total, No.	57	10	23	24	51
Mean (SD)	−0.58 (1.76)	−3.71 (1.27)	−0.50 (0.90)	0.64 (0.54)	−0.38 (1.74)
Nonoverminus group					
Total, No.	52	16	14	22	49
Mean (SD)	−0.29 (1.60)	−2.12 (1.75)	0.13 (0.35)	0.77 (0.35)	−0.19 (1.58)
Change in SER from baseline to 24 mo, mean (SD)[e]					
Overminus group					
Total, No.	57	10	23	24	20
Mean (SD)	−0.61 (0.94)	−1.81 (0.76)	−0.60 (0.88)	−0.01 (0.54)	−0.51 (0.72)
Nonoverminus group					
Total, No.	52	16	14	22	17
Mean (SD)	−0.14 (0.65)	−0.50 (0.99)	0.01 (0.33)	0.03 (0.34)	0.18 (0.84)
>1.00 D of SER myopic change from baseline to 24 mo, No./total No. (%)					
Overminus group	14/57 (25)	8/10 (80)	6/23 (26)	0/24	3/20 (15)
Nonoverminus group	4/52 (8)	4/16 (25)	0/14	0/22	0/17
RR (95% CI)[d]	3.9 (1.6-9.3)	2.9 (1.2-6.9)	NA[d]	NA[d]	NA[d]
Change in SER from 12 to 24 mo, mean (SD)[f]					
Overminus group					
Total, No.	57	10	23	24	33
Mean (SD)	−0.20 (0.55)	−0.75 (0.51)	−0.23 (0.50)	0.06 (0.44)	−0.09 (0.66)
Nonoverminus group					
Total, No.	52	16	14	22	28
Mean (SD)	−0.07 (0.45)	−0.22 (0.59)	−0.03 (0.41)	0.01 (0.33)	0.04 (0.46)

(continued)

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Table 2. Refractive Error During Follow-Up in the Most Myopic Eye at Baseline (continued)

Measure	Overall (cycloplegic refraction)	Baseline SER (cycloplegic refraction)[a]			Overall (cycloplegic autorefraction)[b]
		−0.50 D to −6.00 D	−0.375 D to 0.375 D	0.50 D to 1.00 D	
36 mo					
SER at 36 mo, mean (SD)					
Overminus group					
Total, No.	112	19	43	48	102
Mean (SD)	−0.72 (1.79)	−3.83 (1.53)	−0.64 (0.99)	0.36 (0.75)	−0.74 (1.92)
Nonoverminus group					
Total, No.	91	29	25	37	84
Mean (SD)	−0.56 (1.67)	−2.32 (1.71)	−0.19 (0.78)	0.57 (0.62)	−0.50 (1.74)
Change in SER from baseline to 36 mo, mean (SD)[e]					
Overminus group					
Total, No.	112	19	43	48	38
Mean (SD)	−0.74 (1.00)	−1.86 (1.01)	−0.69 (0.96)	−0.35 (0.70)	−0.83 (0.95)
Nonoverminus group					
Total, No.	91	29	25	37	30
Mean (SD)	−0.44 (0.85)	−0.93 (1.07)	−0.26 (0.67)	−0.18 (0.57)	−0.20 (1.03)
>1.00 D of SER myopic change from baseline to 36 mo, No./total No. (%)					
Overminus group	30/112 (27)	14/19 (74)	13/43 (30)	3/48 (6)	13/38 (34)
Nonoverminus group	14/91 (15)	8/29 (28)	3/25 (12)	3/37 (8)	3/30 (10)
RR (95% CI)[c]	1.8 (1.0-3.0)	2.6 (1.3-5.1)	2.5 (0.8-7.6)	0.7 (0.2-3.4)	4.0 (1.1-14.0)
Change in SER from 12 to 36 mo, mean (SD)[g]					
Overminus group					
Total, No.	112	19	43	48	63
Mean (SD)	−0.34 (0.67)	−0.76 (0.75)	−0.35 (0.70)	−0.15 (0.55)	−0.39 (0.89)
Nonoverminus group					
Total, No.	91	29	25	37	52
Mean (SD)	−0.36 (0.66)	−0.69 (0.82)	−0.22 (0.56)	−0.20 (0.46)	−0.27 (0.66)
Change in SER from 24 to 36 mo, mean (SD)[h]					
Overminus group					
Total, No.	49	6	22	21	45
Mean (SD)	−0.08 (0.41)	−0.02 (0.58)	−0.15 (0.44)	−0.02 (0.33)	−0.30 (0.85)
Nonoverminus group					
Total, No.	48	15	14	19	45
Mean (SD)	−0.26 (0.44)	−0.43 (0.50)	−0.14 (0.48)	−0.20 (0.32)	−0.24 (0.49)

Abbreviations: D, diopter; NA, not applicable; RR, risk ratio; SER, spherical equivalent refractive error.

[a] Subgroups exclude 2 ineligible participants who had an SER greater than 1.00 D at baseline (1.125 D and 1.25 D).

[b] Overall treatment group difference of SER from cycloplegic autorefraction (overminus − nonoverminus) equal to −0.68 D (95% CI, −1.21 to −0.15) at 24 months and −0.66 D (95% CI, −1.15 to −0.17) at 36 months. Difference obtained from an analysis of covariance model adjusted for baseline refractive error in the most myopic eye. Ten participants at 24 months and 2 at 36 months were excluded from the analysis because of visits outside the analysis window.

[c] RR reflects the relative probability of a participant in the overminus group having more than 1.00 D of myopic change compared with a participant in the nonoverminus group.

[d] RR could not be calculated due to the denominator of 0 (ie, no participants in the nonoverminus group had >1.00 D of SER myopic change during the time period).

[e] Overall treatment group difference of change in refractive error from baseline (overminus − nonoverminus) equal to −0.52 D (95% CI, −0.79 to −0.24; $P < .001$) at 24 months and −0.36 D (95% CI, −0.59 to −0.12; $P = .003$) at 36 months. The difference is obtained from an analysis of covariance model adjusted for baseline SER in the most myopic eye. Eleven participants at 24 months and 3 at 36 months were excluded from the analyses due to visits outside the analysis window. For participants whose 24-month visit was outside the analysis window, the 18-month SER was used instead, if available and if completed within the 24-month window.

[f] Overall treatment group difference of change in SER from 12 months to 24 months (overminus − nonoverminus) equal to −0.15 D (95% CI, −0.33 to 0.03). Difference obtained from an analysis of covariance model adjusted for baseline SER in the most myopic eye. Eleven participants were excluded from the analysis due to visits outside the analysis window at 24 months.

[g] Overall treatment group difference of change in SER from 12 months to 36 months (overminus − nonoverminus) equal to −0.001 D (95% CI, −0.18 to 0.18). Difference obtained from an analysis of covariance model adjusted for baseline SER in the most myopic eye. Three participants were excluded from the analysis due to visits outside the analysis window at 36 months.

[h] Overall treatment group difference of change in SER from 24 months to 36 months (overminus − nonoverminus) equal to 0.16 D (95% CI, −0.02 to 0.34). Difference obtained from an analysis of covariance model adjusted for baseline SER in the most myopic eye. Eleven participants were excluded from the analysis due to visits outside the analysis window at 24 months.

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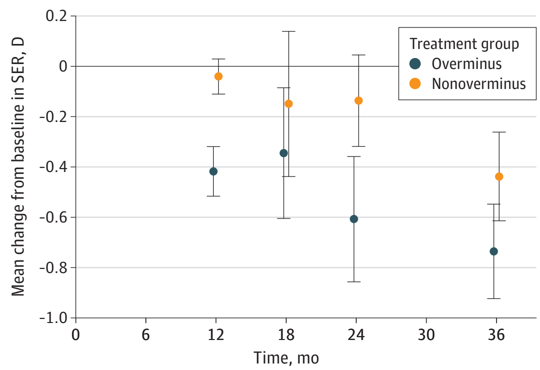
Figure 2. Mean Change in Spherical Equivalent Refractive Error (SER) by Treatment Group Over 36 Months



No. at risk	12	18	24	36
Overminus	189	34	57	112
Nonoverminus	169	25	52	91

The change from baseline in SER (diopters [D]) are shown at each visit by treatment group. Participants in the overminus group received full treatment (spectacles of −2.50 D) from months 0 to 12, half treatment (spectacles of −1.25 D) from months 12 to 15, and no treatment from months 15 to 18. Treatment was at investigator discretion from months 18 to 36 for participants in both the overminus and nonoverminus groups. The number of participants at 18 months was smaller because the cycloplegic refraction was implemented for the remaining 18-month visits after the discontinuation of overminus lenses, which was 2 years and 10 months after the randomized clinical trial commenced (10 months after enrollment ended) after the data and safety monitoring committee observed greater myopic shift over 12 months in the overminus group. Error bars indicate 95% CIs.

each time point was similar in participants who completed the visit being analyzed (ie, regardless of which other follow-up visits were completed) (**Figure 2**) and in the subset of participants who completed both the 24-month and 36-month visits (eFigure 1 in Supplement 3).

Cycloplegic autorefraction measurements of change in SER from baseline were available for 37 of 109 (33.9%) and 68 of 205 (33.2%) who completed the 24-month and 36-month visits, respectively. The SER changes by cycloplegic autorefraction were similar to those by cycloplegic retinoscopy (Table 2).

Biometry Measures (Secondary Outcomes)

Axial length data were available for 84 of 109 participants (77.1%) at 24 months and 162 of 205 (79.0%) at 36 months. Mean (SD) axial length was not significantly different between treatment groups at 24 months (overminus, 23.45 [1.09] mm; nonoverminus, 23.27 [0.88] mm; difference, 0.25 mm; 95% CI, −0.37 to 0.86; $P = .63$) or 36 months (overminus, 23.66 [1.11] mm; nonoverminus, 23.41 [0.87] mm; adjusted difference, 0.24 mm; 95% CI, −0.17 to 0.65; $P = .58$) (**Table 3**). There were no significant treatment group differences for flat corneal curvature, anterior chamber depth, or lens thickness at 24 or 36 months (Table 3).

Exotropia Control, Exotropia Magnitude, and Near Stereoacuity (Exploratory Outcomes)

There were no significant treatment group differences for IXT control (distance or near), magnitude of exodeviation (distance or near), or near stereoacuity at 24 or 36 months (eTables 1 and 3 and eFigure 2 in Supplement 3).

Treatment Used During the Extension Study

Between 19 and 36 months, 15 of 124 (12.1%) in the overminus group and 13 of 99 (13%) in the nonoverminus group had surgery for their IXT. The percentages of participants who received other types of IXT treatments during this time were similar between the 2 groups (eTable 2 in Supplement 3), including overminus spectacles being restarted in 14 of 124 (11.3%) in the overminus group and being used for the first time in 11 of 99 (11%) in the nonoverminus group. Myopia control treatments were used in 2 of 124 (1.6%) and 1 of 99 (1%) in the overminus and nonoverminus groups, respectively (eTable 4 in Supplement 3).

Discussion

We previously reported a greater myopic shift over 1 year of overminus spectacles (−2.50 D) compared with nonoverminus spectacles in children with IXT aged 3 to 10 years.[12] The current post-RCT extension study found that the treatment group difference of 0.37 D (95% CI, −0.49 to −0.26) in myopic shift at 1 year persisted but did not increase further during the 2 years after the start of weaning and discontinuation of overminus treatment. Thus, the same treatment group difference initially observed at 12 months was still present at 3 years. These findings suggest that cessation of the original overminus lens treatment neither exacerbated nor lessened the myopic shift.

Previous studies on overminus lens treatment for IXT have not found a myopic shift greater than what would be considered age expected. A randomized trial[11] evaluating −2.50-D overminus lenses combined with 4-Δ base-in prism in 60 children aged 3 to 6 years with IXT and hyperopia from 0.50 to 5.00 D found no significant change in refractive error in both treatment and observation groups at 1 year. In another RCT[18,19] using an algorithm to customize overminus lens power based on the child's distance exodeviation control and magnitude, accommodative convergence to convergence ratio, and refractive error showed no difference in refractive and biometric changes between the overminus (lens range of −1.00 to −6.25 D) and observation groups at 6 months in 84 children aged 4 to 15 years with IXT and refractive error between 3.00 and −6.00 D. There are numerous possible reasons for the discordant study results between our original RCT and these 2 RCTs, including differences in overminus lens power or prescribing strategy used, participant age, refractive error eligibility criteria, length of follow-up during and after treatment, and sample size. For example, neither of the other RCTs followed up with their participants after discontinuing overminus spectacles, and our study's larger sample size resulted in higher statistical power to detect differences between treatment groups. Other studies[8,19-23] of overminus spectacles are retrospective and without control groups and have concluded overminus spectacles are associated with no more than age-expected myopic shift.

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Table 3. Biometry Measures at 24 and 36 Months From Randomization

	24 mo								36 mo							
			Baseline SER subgroups[a]								Baseline SER subgroups[a]					
	Overall		−0.50 to −6.00 D		−0.375 to 0.375 D		0.50 to 1.00 D[b]		Overall		−0.50 to −6.00 D		−0.375 to 0.375 D		0.50 to 1.00 D[b]	
Measure	Overminus	Nonover-minus	Overminus	Nonover-minus	Overminus	Nonover-minus	Overminus	Nonover-minus	Overminus	Nonover-minus	Overminus	Nonover-minus	Overminus	Nonover-minus	Overminus	Nonover-minus
Axial length																
Total, No.	40	44	5	15	16	12	19	17	86	76	17	26	32	23	35	26
Mean (SD), mm	23.45 (1.09)	23.27 (0.88)	25.04 (1.49)	23.86 (0.88)	23.48 (0.82)	22.94 (0.93)	23.02 (0.78)	22.98 (0.58)	23.66 (1.11)	23.41 (0.87)	24.94 (1.03)	23.99 (0.78)	23.61 (0.89)	23.24 (0.87)	23.11 (0.84)	23.00 (0.66)
Median (range), mm	23.16 (21.69 to 27.43)	23.25 (21.43 to 25.92)	24.70 (23.79 to 27.43)	23.73 (22.77 to 25.92)	23.30 (22.23 to 25.00)	22.85 (21.43 to 24.55)	23.00 (21.69 to 24.76)	22.96 (21.89 to 24.07)	23.52 (21.90 to 27.53)	23.35 (21.69 to 25.47)	24.84 (23.22 to 27.53)	23.83 (22.76 to 25.47)	23.45 (22.18 to 25.67)	23.19 (21.69 to 24.86)	22.93 (21.90 to 24.78)	22.96 (21.88 to 24.31)
Treatment group difference, mean (95% CI)[c]	0.25 (−0.37 to 0.86)		NA		NA		NA		0.24 (−0.17 to 0.65)		NA		NA		NA	
P value	.63		NA		NA		NA		.58		NA		NA		NA	
Flat corneal curvature																
Total, No.	37	39	5	15	14	10	18	14	77	68	16	24	31	21	29	23
Mean (SD), D	42.75 (1.62)	43.23 (1.43)	41.78 (2.00)	42.95 (0.96)	43.01 (1.55)	43.61 (1.91)	42.83 (1.57)	43.27 (1.51)	42.86 (1.77)	43.09 (1.42)	42.35 (2.06)	42.79 (1.01)	42.87 (1.65)	43.04 (1.67)	43.11 (1.77)	43.46 (1.51)
Median (range), D	42.99 (38.84 to 46.29)	43.29 (40.25 to 47.02)	42.33 (38.84 to 43.67)	43.16 (41.11 to 44.49)	43.05 (39.35 to 46.29)	43.67 (40.61 to 47.02)	42.70 (40.04 to 46.08)	43.37 (40.25 to 45.70)	43.09 (37.80 to 46.67)	43.07 (40.13 to 46.97)	42.95 (37.80 to 45.79)	42.97 (40.61 to 45.25)	42.83 (38.40 to 46.67)	42.53 (40.56 to 46.97)	43.15 (40.02 to 46.43)	43.72 (40.13 to 45.86)
Treatment group difference, mean (95% CI)[c]	−0.57 (−1.58 to 0.44)		NA		NA		NA		−0.20 (−0.90 to 0.49)		NA		NA		NA	
P value	.58		NA		NA		NA		.63		NA		NA		NA	
Anterior chamber depth																
Total, No.	33	38	5	13	13	10	15	15	78	68	16	24	27	20	33	23
Mean (SD), mm	3.74 (0.26)	3.72 (0.30)	3.90 (0.26)	3.79 (0.11)	3.81 (0.26)	3.75 (0.16)	3.62 (0.23)	3.65 (0.45)	3.67 (0.29)	3.70 (0.26)	3.79 (0.31)	3.76 (0.21)	3.69 (0.26)	3.65 (0.26)	3.58 (0.26)	3.70 (0.29)
Median (range), mm	3.71 (3.24 to 4.20)	3.74 (3.00 to 4.69)	3.88 (3.57 to 4.20)	3.78 (3.61 to 4.03)	3.79 (3.35 to 4.17)	3.75 (3.55 to 3.99)	3.59 (3.24 to 4.08)	3.60 (3.00 to 4.69)	3.68 (3.13 to 4.32)	3.71 (3.15 to 4.47)	3.81 (3.15 to 4.27)	3.79 (3.33 to 4.33)	3.65 (3.13 to 4.24)	3.64 (3.15 to 4.03)	3.57 (3.18 to 4.03)	3.64 (3.29 to 4.47)
Treatment group difference, mean (95% CI)[c]	0.02 (−0.17 to 0.20)		NA		NA		NA		−0.03 (−0.15 to 0.08)		NA		NA		NA	
P value	.81		NA		NA		NA		.63		NA		NA		NA	
Lens thickness[d]																
Total, No.	20	22	5	8	6	5	9	9	46	35	11	16	13	9	20	9
Mean (SD), mm	3.39 (0.14)	3.41 (0.13)	3.40 (0.18)	3.41 (0.10)	3.37 (0.15)	3.41 (0.12)	3.41 (0.13)	3.42 (0.17)	3.40 (0.12)	3.42 (0.18)	3.41 (0.12)	3.39 (0.15)	3.40 (0.13)	3.44 (0.12)	3.39 (0.12)	3.38 (0.15)

(continued)

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Table 3. Biometry Measures at 24 and 36 Months From Randomization (continued)

Measure	24 mo								36 mo							
	Overall		Baseline SER subgroups[a]						Overall		Baseline SER subgroups[a]					
			−0.50 to −6.00 D		−0.375 to 0.375 D		0.50 to 1.00 D[b]				−0.50 to −6.00 D		−0.375 to 0.375 D		0.50 to 1.00 D[b]	
	Overminus	Nonoverminus	Overminus	Nonoverminus	Overminus	Nonoverminus	Overminus	Nonoverminus	Overminus	Nonoverminus	Overminus	Nonoverminus	Overminus	Nonoverminus	Overminus	Nonoverminus
Median (range), mm	3.43 (3.18 to 3.67)	3.40 (3.21 to 3.70)	3.38 (3.22 to 3.67)	3.41 (3.24 to 3.56)	3.37 (3.18 to 3.55)	3.42 (3.27 to 3.55)	3.44 (3.22 to 3.57)	3.34 (3.21 to 3.70)	3.40 (3.14 to 3.68)	3.42 (2.98 to 4.10)	3.40 (3.25 to 3.68)	3.41 (2.98 to 3.59)	3.42 (3.14 to 3.60)	3.46 (3.25 to 3.62)	3.36 (3.22 to 3.65)	3.34 (3.15 to 3.60)
Treatment group difference, mean (95% CI)[c]	−0.03 (−0.15 to 0.09)		NA		NA		NA		−0.02 (−0.11 to 0.07)		NA		NA		NA	
P value	.63		NA		NA		NA		.63		NA		NA		NA	

Abbreviations: D, diopter; NA, not applicable; SER, spherical equivalent refractive error.

[a] Treatment group differences were not calculated for baseline subgroups due to limited sample size.

[b] Subgroups exclude 2 ineligible participants who had an SER greater than 1.00 D at baseline (1.125 D and 1.25 D).

[c] Treatment group differences were obtained from an analysis of variance model; we could not adjust for the baseline values of each measure because biometry measures were not collected at baseline. 95% CIs and *P* values were adjusted to control the false discovery rate at 5%. A total of 9, 8, 7, and 5 participants were excluded from the analysis of axial length, flat corneal radius, anterior chamber depth, and lens thickness, respectively, due to visits outside the analysis window at 24 months. One participant was excluded from the analysis of axial length, flat corneal radius, and anterior chamber depth due to visits outside the analysis window at 36 months.

[d] Lens thickness was only available at the subset of sites with measurement capabilities.

In the current study, participants in the overminus group had approximately twice the risk of myopic progression greater than 1 D over 3 years vs those in the nonoverminus group. The difference in myopic shift between the overminus and nonoverminus groups was greatest in participants with baseline myopia (−0.50 to −6.00 D). Because myopia typically progresses within the age range of our participants, it was not surprising that both groups continued to progress in the myopic direction after treatment was discontinued. The myopia progression from 12 to 36 months in participants with myopia at baseline in both groups was comparable with the mean myopia progression in cohorts of children with myopia without IXT,[24,25] suggesting temporary use of overminus spectacles does not accelerate myopia progression after discontinuing treatment.

The current leading theory for myopia progression is that peripheral hyperopic retinal defocus drives axial elongation[26,27]; however, this hypothesis is not universally accepted.[28] The mechanism by which overminus lens treatment caused an increase in myopic shift in our study cohort with IXT is unknown. Children wearing overminus lenses need to accommodate to see clearly through the overminus lenses, and the more prolate eye shape induced by accommodation could lead to changes in relative peripheral refraction[29] and faster myopia progression. Another speculation is that participants wearing overminus spectacles might exhibit greater accommodative lag, resulting in light being focused behind the retina during near work, which may act as a signal to increase eye growth and cause myopia progression.[30] Although a previous study has shown that patients with myopia exhibit a larger accommodative lag than patients without myopia,[31] other studies report that accommodative lag is unrelated to myopia progression.[32-35] Because we did not measure peripheral refraction or accommodative accuracy in the present study, we cannot evaluate the association between these factors and myopic shift associated with overminus lens treatment.

Despite finding a greater mean myopic shift from baseline to 24 and 36 months in the overminus group, we found no statistically significant differences in axial length between treatment groups. However, because only approximately 40% of the original RCT participants had axial length measured, resulting in wide 95% CIs, we cannot exclude clinically meaningful differences between treatment groups. We did not measure axial length at baseline and 12 months, precluding us from adjusting this analysis for any potential baseline imbalances in axial length and from determining the axial length increase over time, which we would expect to be associated with a myopic shift. There were also no statistically significant differences between treatment groups for flat corneal curvature, anterior chamber depth, or lens thickness at 24 or 36 months.

The findings from our RCT and extension study suggest that children with IXT and baseline hyperopia of 0.50 to 1.00 D do not have significant risk for a myopic shift greater than 1.00 D with overminus lens treatment over 36 months. This finding is consistent with a RCT[11] of combined overminus lens and base-in prism treatment for children with IXT and hyperopia, which reported similar mean (SD) refractive errors of 1.42

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(1.25) D in the observation group (n = 30) and 1.43 (1.12) D in the combined treatment group (n = 28) at 12 months.

There were no differences in distance IXT control, exodeviation magnitude, or stereoacuity between treatment groups at 24 or 36 months. These findings are unsurprising given that the RCT found that the improved exotropia control shown after 12 months of overminus did not persist at 18 months.

Limitations

This study has several limitations. Only 53% of the original RCT cohort completed the 36-month visit, which could result in selection bias if participants who completed the study differed from those who did not in known or unknown factors; nevertheless, baseline demographic and clinical characteristics and mean SER at 12 months appear similar between these groups. When the post-RCT extension study was initiated, nearly one-half the participants had already passed their 24-month visit window, contributing to smaller sample sizes at 24 months. However, the proportions of RCT participants completing the 24-month visit were similar between groups (57 of 196 [29.1%] in the overminus group and 52 of 190 [27.4%] in the nonoverminus group) and the proportions completing the final 36-month visit were similar between groups and nearly twice as high (112 [57.1%] in the overminus group and 93 [48.9%] in the nonoverminus group). Subgroup analyses should be interpreted with caution because of small sample sizes in baseline SER subgroups. Investigators performing cycloplegic retinoscopy were not masked to participants' treatment assignments, potentially leading to bias; however, the subset with autorefraction showed similar results. Additionally, we did not collect biometry measures, particularly axial length, at baseline or 12 months, which limits the power of the analyses and precludes adjustment for potential confounding.

Conclusions

In conclusion, the myopic shift associated with 1 year of −2.50-D overminus lens treatment persisted 2 years after discontinuing overminus lens treatment. Both overminus and nonoverminus groups had similar myopic shift during the 2-year period after the start of treatment weaning and cessation. Over 3 years, 1 year of overminus treatment was associated with a 0.33-D increase in mean myopic shift and approximately twice the risk of having a myopic shift of 1.00 D or greater. The risk of myopic shift should be discussed when considering overminus lens treatment for children with IXT, particularly for those already myopic.

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IXT6 – A Pilot Randomized Clinical Trial of Base-in Relieving Prism Spectacle Treatment for Intermittent Exotropia.

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CLINICAL TRIAL

A Pilot Randomized Clinical Trial of Base-in Relieving Prism Spectacle Treatment of Intermittent Exotropia

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SIGNIFICANCE: This pilot randomized trial, the first to evaluate a specific base-in relieving prism treatment strategy for childhood intermittent exotropia, did not support proceeding to a full-scale clinical trial. Defining and measuring prism adaptation in children with intermittent exotropia are challenging and need further study.

PURPOSE: This study aimed to determine whether to proceed to a full-scale trial of relieving base-in prism spectacles versus refractive correction alone for children with intermittent exotropia.

METHODS: Children 3 years old to those younger than 13 years with distance intermittent exotropia control score of ≥2 points on the Intermittent Exotropia Office Control Scale (Strabismus 2006;14:147–150; 0 [phoria] to 5 [constant]), ≥1 episode of spontaneous exotropia, and 16 to 35Δ by prism-and-alternate-cover test, who did not fully prism adapt on a 30-minute in-office prism-adaptation test were randomized to base-in relieving prism (40% of the larger of distance and near exodeviations) or nonprism spectacles for 8 weeks. A priori criteria to conduct a full-scale trial were defined for the adjusted treatment group difference in mean distance control: "proceed" (≥0.75 points favoring prism), "uncertain" (>0 to <0.75 points favoring prism), or "do not proceed" (≥0 points favoring nonprism).

RESULTS: Fifty-seven children (mean age, 6.6 ± 2.2 years; mean baseline distance control, 3.5 points) received prism (n = 28) or nonprism (n = 29) spectacles. At 8 weeks, mean control values were 3.6 and 3.3 points in prism (n = 25) and nonprism (n = 25) groups, respectively, with an adjusted difference of 0.3 points (95% confidence interval, –0.5 to 1.1 points) favoring nonprism (meeting our a priori "do not proceed" criterion).

CONCLUSIONS: Base-in prism spectacles, equal to 40% of the larger of the exodeviations at distance or near, worn for 8 weeks by 3- to 12-year-old children with intermittent exotropia did not yield better distance control than refractive correction alone, with the confidence interval indicating that a favorable effect of 0.75 points or larger is unlikely. There was insufficient evidence to warrant a full-scale randomized trial.

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Intermittent exotropia is a common form of strabismus characterized by periods of exotropia interspersed with periods of normal ocular alignment. Nonsurgical management options beyond refractive correction are part-time patching,[1,2] over-minus lenses,[3,4] vision therapy/orthoptics,[5,6] and spectacles with base-in prism equal to (i.e., corrective) or less than (i.e., relieving or partial) the strabismic angle.[7–9] Relieving prism treatment is prescribed for intermittent exotropia with the rationale of potentially restoring, improving, or maintaining normal binocular vision by optically reducing the fusional convergence demand, thus making it easier to sustain fusion.[7–9]

If prism treatment results in better control of the intermittent exotropia and facilitates enhanced binocular fusion, thereby reducing the need for surgical or vision therapy/orthoptic treatment, there could be significant cost savings. In the absence of published

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reports evaluating the effectiveness of base-in relieving prism for intermittent exotropia, the Pediatric Eye Disease Investigator Group designed a pilot randomized controlled trial to determine whether a full-scale randomized trial should be conducted.

The objective of this 8-week pilot randomized trial was to compare spectacles with relieving prism with spectacles without prism in controlling intermittent exotropia. Our goals were to determine whether to proceed to a full-scale trial by evaluating the short-term effect of relieving prism treatment on distance control of the intermittent exotropia and to assess feasibility aspects of recruitment, retention, treatment adherence, and masking. We also ascertained the proportion of participants reporting good to excellent adherence with wearing prism spectacles and the incidence of associated adverse effects.

METHODS

The study was conducted according to the tenets of the Declaration of Helsinki[10] by the Pediatric Eye Disease Investigator Group at 28 clinical sites. The protocol[11] and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by the required institutional review boards. A parent or guardian of each participant gave written informed consent, and participants gave written assent when required. An independent Data and Safety Monitoring Committee provided oversight. This study followed the Consolidated Standards of Reporting Trials reporting guideline[12] and is listed on www.ClinicalTrials.gov.[13]

Eligibility Criteria

Eligible children were 3 years old to those younger than 13 years with intermittent exotropia meeting the following criteria: (1) intermittent or constant exotropia at distance with an Intermittent Exotropia Office Control Score[14] of 2.0 points or worse on a scale ranging from 0 (phoria) to 5 (constant), with at least 1 score of 3, 4, or 5 (i.e., spontaneous tropia; Appendix 1, available at http://links.lww.com/OPX/A607); (2) exodeviation of 16 to 35 prism diopters (Δ) at distance and 10 to 35Δ at near measured by the prism-and-alternate-cover test with the near exodeviation not exceeding the distance exodeviation by more than 10Δ; and (3) no prior use of prism spectacles. Additional eligibility criteria are shown in Appendix 2, available at http://links.lww.com/OPX/A608.[15,16]

Enrollment Testing

Before clinical testing, participants completed the Child Intermittent Exotropia Symptom Questionnaire[17,18] (Appendix 3, available at http://links.lww.com/OPX/A609), and parents completed a seven-item survey (Appendix 4, available at http://links.lww.com/OPX/A610) assessing potential issues with spectacles. Testing was performed sequentially by the same study-certified examiner through the participant's habitual optical correction as follows: control 1 (Appendix 1, available at http://links.lww.com/OPX/A607), near stereoacuity; control 2, cover-uncover test, and distance and near prism-and-alternate-cover tests (20/40 optotype at 6 m and 20/30 optotype at 33 cm); control 3, density of suppression (described in Table 1, footnote).[19] Distance visual acuity was measured using the investigator's usual optotype method.

Prism Adaptation Testing at Enrollment

After clinical testing and before randomization, an in-office prism adaptation test was administered so that children with "full" prism adaptation (i.e., deviation magnitude increases by the prism magnitude worn) would be excluded from the trial. The prism power to be prescribed if the participant were to be randomized to the prism group (40% of the larger deviation; see Treatment Regimens) was split equally (7Δ split as 3 and 4Δ) between the eyes and placed in a trial frame with the refractive correction, which the child wore for at least 30 minutes. Afterward, a near cover-uncover test was performed, and the distance and near prism-and-alternate-cover tests were measured through the trial-framed lenses and prisms. Children with full prism adaptation, any new esotropia at near, or a near esodeviation ≥6Δ were not eligible for randomization. Test procedure details are specified in the *Intermittent Exotropia-6 Testing Procedures Manual* (e-Supplement 1, available at http://links.lww.com/OPX/A611).

Treatment Regimens

Eligible participants were randomly assigned 1:1 through the study website to either prism or nonprism spectacles, using a permuted block design stratified by the mean of three measures of distance control (2 to <3, 3 to <4, and 4 to 5 points). Prism group participants were prescribed spectacles with their refractive correction and ground-in base-in prism equal to 40% of the larger of the distance and near exodeviations (6Δ for a 16Δ exodeviation, 7Δ for 18Δ, 8Δ for 20Δ, 10Δ for 25Δ, 12Δ for 30Δ, and 14Δ for 35Δ) divided equally between the eyes. This prism magnitude (40% of the larger deviation) was the consensus opinion of the study planning committee after reviewing published guidelines.[7,9,20] Nonprism group participants were prescribed spectacles with refractive correction only. Astigmatism, anisometropia, and myopia were fully corrected based on cycloplegic refraction within 7 months of enrollment. For spherical equivalent hyperopia or emmetropia, the sphere power resulting in plano spherical equivalent was prescribed for the less hyperopic eye, with a symmetrical reduction of hyperopic sphere power for the fellow eye (e.g., cycloplegic refraction of +3.00 −1.00 × 180 and +2.00 −2.00 × 175 resulted in a prescription of +2.00 −1.00 × 180 and +1.00 −2.00 × 175 for the right and left eyes, respectively). No other treatment of intermittent exotropia was allowed.

Masking

To facilitate masking, families were not informed of the child's treatment assignment, and the dispensing optician was instructed not to disclose the prescription. Examiners masked to treatment assignment were not apprised of the child's refractive error or spectacle prescription, did not handle the study spectacles, and were queried after their examinations whether they had been unmasked to treatment assignment.

Follow-up Including Primary Outcome Examination

Follow-up (timed from randomization) consisted of a telephone call at 3 weeks to verify receipt of study spectacles and the primary outcome visit at 8 weeks (±2 weeks). Because the coronavirus 2019 pandemic resulted in restrictions on clinical research visits, the Data and Safety Monitoring Committee approved an amended protocol (April 2020) that allowed participants to continue treatment and extended the primary outcome visit window to 24 weeks.

At outcome, adherence with spectacle wear was determined to be excellent (>75% of waking hours), good (51 to 75%), fair (26 to 50%), or poor (≤25%) based on home calendar review and parental report. The Child Intermittent Exotropia Symptom Questionnaire[17,18] (Appendix 3, available at http://links.lww.com/OPX/A609) and the

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TABLE 1. Baseline demographic and clinical characteristics by treatment group (N = 57)

	Prism (n = 28)		Nonprism (n = 29)	
	n	%	n	%
Sex: female	17	61	16	55
Race/ethnicity				
Asian	0	0	3	10
Black/African American	6	21	2	7
Hispanic	4	14	7	24
White	16	57	17	59
More than one race	2	7	0	0
Age at randomization (y)				
3–<5	10	36	7	24
5–<7	7	25	10	34
7–<9	8	29	8	28
≥9	3	11	4	14
Mean (SD)	6.4 (2.4)		6.8 (2.1)	
Range	3.2–12.3		3.7–12.6	
Refractive error, average of eyes (spherical equivalent; D)				
−6.00 to <−2.00	2	7	2	7
−2.00 to <−1.00	2	7	0	0
−1.00 to <−0.00	2	7	6	21
0.00 to <1.00	14	50	13	45
1.00 to <2.00	7	25	8	28
Median (range)	0.6 (−3.80 to +2.0)		0.5 (−4.00 to +1.80)	
Mean (SD)	0.2 (1.3)		0.2 (1.3)	
Prior IXT treatment				
Overminus	2	7	3	10
Patching	7	25	5	17
Patching and atropine	0	0	1	3
Patching and overminus	1	4	0	0
Vision therapy and overminus	0	0	1	3
None	18	64	19	66
Near stereoacuity in arc seconds (log arcsec)*				
40 (1.60)	2	7	3	10
60 (1.78)	6	21	8	28
100 (2.00)	9	32	7	24
200 (2.30)	3	11	4	14
400 (2.60)	5	18	3	10
800 (2.90)	2	7	2	7
Nil (3.10)	1	4	2	7
Median (range)	2.0 (1.6–3.2)		2.0 (1.6–3.2)	
Mean (SD)	2.2 (0.4)		2.2 (0.5)	
Suppression†				
Negligible (0)	3	12	3	12
Mild (1)	1	4	4	16
Moderate (2)	4	15	8	32
Dense (3)	18	69	10	40

*Randot Preschool Stereoacuity test (Stereo Optical Co., Inc., Chicago, IL). For analysis, stereoacuity was converted from seconds of arc scores to log arcsec values (in parentheses) as follows: 40 (1.60), 60 (1.78), 100 (2.00), 200 (2.30), 400 (2.60), and 800 (2.90); participants with no detectable (nil) stereoacuity were assigned the value of 1600 (3.20). †The Office Suppression Test[19] is a three-step procedure to grade density of suppression in patients with intermittent exotropia who are manifestly exotropic. During an episode of manifest exotropia (spontaneous or induced), the participant viewed a 20/50 optotype at 6 m, in normal room illumination, and was asked whether one or two letters were seen. If two letters were reported, suppression was classified as "negligible" (grade of 0). If one letter was reported (indicating suppression), a single-point light source was viewed at 6 m with a red filter placed over the habitually fixing eye. If two lights were reported (one white and one red), suppression was classified as "mild" (grade 1). If one light was reported, the light source was viewed again in dim lighting with a red filter over the preferred eye. Suppression was classified as "moderate" (grade 2) if two lights were reported or dense (grade 3) if one light was reported. "Missing" refers to cases in which participants were unable to understand the test and/or gave unreliable responses. D = diopters; IXT = intermittent exotropia; log arcsec = logarithm of arc seconds; SD = standard deviation; y = years.

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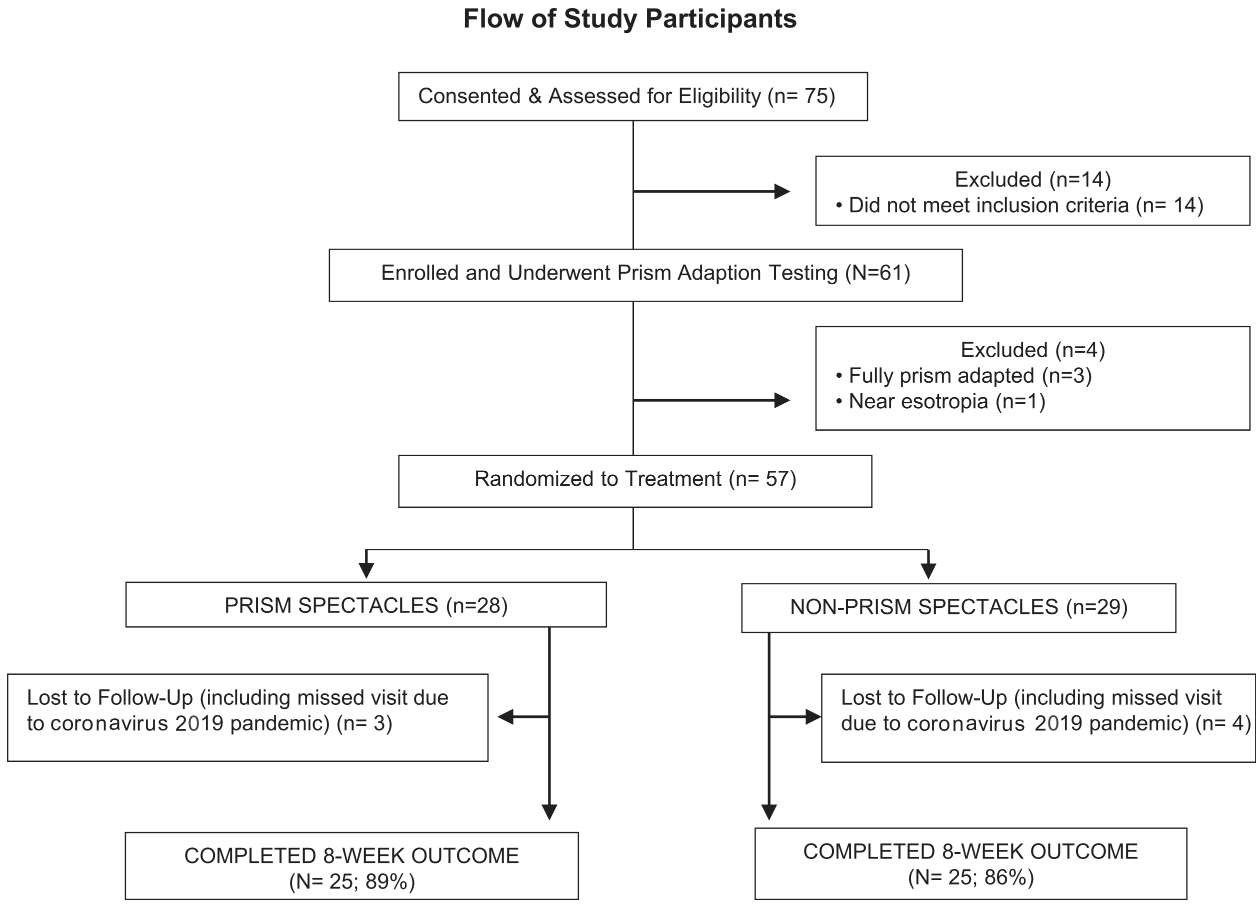

FIGURE 1. Flow of study participants. Recruitment ended early because of COVID-19 pandemic; therefore, there were 7 fewer randomized participants than planned.

Parent Spectacle Symptom Survey (Appendix 4, available at http://links.lww.com/OPX/A610) were administered, and a masked examiner completed the same clinical testing performed at enrollment, with participants wearing their study spectacles. When study spectacles were unavailable, a trial frame and trial lenses with the imprinted prism and dioptric power designations concealed were used.

Statistical Methods

Prism Adaptation: Testing and Determination

For the prism adaptation test at enrollment, the in-prism exodeviation magnitude measurement used for analysis was defined as the prism-and-alternate-cover test measured through the trial-framed prism (the sum of prism in the trial frame and the measuring prism held in front of the trial frame needed to neutralize the deviation). For example, if 10Δ of base-in prism was placed in the trial frame and the measuring prism required to neutralize the deviation with the trial-framed 10Δ base-in prism remaining in place measured 25Δ base-in, then the total in-prism exodeviation magnitude was 35Δ. Full prism adaptation was defined a priori as a total in-prism exodeviation magnitude that equaled or exceeded the sum of the pre-prism measurement of the prism-and-alternate-cover test and the magnitude of base-in prism in the trial frame, at both distance and near. The proportion of pre-randomized participants having full prism adaptation was calculated with an exact 95% confidence interval (CI).

Primary Analysis

The planned convenience sample size of 64 was expected to provide outcome data for at least 60 participants (30 per group). The primary analysis was the treatment group difference (prism minus nonprism [negative difference favors prism] and 95% CI) in mean distance control at the 8-week outcome visit using an analysis of covariance (ANCOVA) adjusted for baseline distance control. Likelihood-based methods were used to account for missing 8-week outcomes. The following a priori criteria, based on the estimated treatment group mean difference, were established for advancing to a full-scale trial: "proceed" (≥0.75 points favoring prism), "uncertain" (>0 to <0.75 points favoring prism), or "do not proceed" (≥0 points favoring nonprism).

Three sensitivity analyses were conducted: (1) limited to participants who received their study spectacles at least 4 weeks before the outcome visit, (2) limited to participants evaluated in study spectacles (vs. trial frame) at outcome, and (3) including all participants and adjusting for baseline near control and baseline distance control.

Secondary Analyses

Two additional analyses were performed for the distance control outcome. Treatment-group differences and 95% CIs were calculated for the proportion of participants with a treatment response (i.e., ≥1 point improvement in mean distance control between baseline and outcome) and the proportion without a spontaneous

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tropia (i.e., did not score 3, 4, or 5 on any control assessment at distance or near).

For each continuous secondary outcome (treatment group comparisons of near control, near stereoacuity, and exodeviation magnitude at distance and near), we calculated the mean treatment group difference at 8 weeks (prism minus nonprism) using ANCOVA models parallel to the primary outcome. The distribution of each outcome and the change between baseline and outcome were tabulated for each treatment group. The total exodeviation (i.e., the sum of ground-in spectacle prism and measuring prism held in front of the spectacles to neutralize the prism-and-alternate-cover test) was used for analysis. As a post hoc outcome in the prism group only, full prism adaptation for 8 weeks was assessed by comparing (1) the total in-prism exodeviation magnitude measurements at 8 weeks (prism magnitude worn added to the prism-and-alternate-cover test measurements using loose prism) at distance and near with (2) the baseline prism-and-alternate-cover test measurements (in spectacles without prism).

An additional post hoc analysis of the Rasch-calibrated Child Intermittent Exotropia Symptom Questionnaire was conducted, calculating overall mean scores for each group at 8 weeks, based on published methods,[18] with scores ranging from 0 (no symptoms) to 100 (worst symptoms). The mean scores were compared using ANCOVA adjusting for baseline scores.

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). No adjustments were made for multiplicity because of the exploratory nature of the analyses.

RESULTS

Prism Adaptation Test at Enrollment

Between September 2019 and March 2020, 61 children with intermittent exotropia underwent in-office pre-randomization prism adaptation testing (Fig. 1). Three participants (5%; 95% CI, 1 to 14%) met the a priori definition of full prism adaptation, and one demonstrated a near esotropia through the prisms in the trial frame. These four participants were excluded from randomization.

Baseline Characteristics of Participants Randomized

Of the 57 participants randomized, 28 were assigned prism and 29 nonprism spectacles. Mean age was 6.6 (±2.2) years, and 33 (58%) were female. Baseline characteristics by treatment group are provided in Table 1. The mean control score at enrollment was 3.5 points at distance and 1.7 points at near in the nonprism

TABLE 2. Baseline exotropia control score and magnitude of deviation by treatment group (N = 57)

	Distance				Near			
	Prism (n = 28)		Nonprism (n = 29)		Prism (n = 28)		Nonprism (n = 29)	
	n	%	n	%	n	%	n	%
Exotropia control* (points)								
0–<1	—	—	—	—	2	7	6	21
1–<2	—	—	—	—	9	32	9	31
2–<3	8	29	8	28	6	21	9	31
3–<4	10	36	10	34	6	21	4	14
4–5	10	36	11	38	5	18	1	3
Mean (SD)	3.4 (0.9)		3.5 (0.9)		2.3 (1.3)		1.7 (1.1)	
Range	2–5		2–5		0–4.3		0–4	
Exodeviation by PACT (in habitual correction; Δ)†								
No exodeviation (orthophoria)	—	—	—	—	—	—	—	—
1–9	—	—	—	—	—	—	—	—
10–15	—	—	—	—	2	7	6	21
16–18	3	11	5	17	8	29	7	24
20–25	18	64	15	52	15	54	8	28
30–35	7	25	9	31	3	11	8	28
40–45	—	—	—	—	—	—	—	—
Mean (SD)	25.1 (4.7)		24.9 (5.6)		21.5 (5.1)		21.1 (7.5)	
Range	16–35		16–35		14–35		10–35	

*Mean of three assessments performed throughout the examination. Mean distance exotropia control of 2 points or greater (worse) was required for eligibility. Mean near exotropia control of less than 5 points (i.e., could not be constant on all three measures) was required for eligibility. †Eligibility criteria: distance exodeviation at least 16Δ measured by PACT and no larger than 35Δ. Near exodeviation at least 10Δ measured by PACT and no larger than 35Δ. Near deviation does not exceed the distance deviation by more than 10Δ by PACT. — indicates not applicable. Δ = prism diopter; PACT = prism-and-alternate-cover test; SD = standard deviation.

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TABLE 3. Exotropia control score at the 8-week outcome visit (N = 50)*

	Distance				Near			
	Prism† (n = 25)		Nonprism‡ (n = 25)		Prism† (n = 25)		Nonprism‡ (n = 25)	
	n	%	n	%	n	%	n	%
Control score (points)								
0–<1	1	4	1	4	5	20	7	28
1–<2	1	4	3	12	9	36	7	28
2–<3	6	24	5	20	7	28	6	24
3–<4	2	8	6	24	3	12	3	12
4–5	15	60	10	40	1	4	2	8
Mean (SD)	3.6 (1.3)		3.3 (1.5)		1.7 (1.1)		1.7 (1.3)	
Range	0.7–5.0		0.0–5.0		0.0–4.0		0.0–5.0	
Adjusted difference in means (95% CI)§	0.3 (–0.5 to 1.1)				0.01 (–0.7 to 0.7)			
Change from baseline to outcome (points)‖								
Mean (SD)	0.1 (1.4)		–0.2 (1.5)		–0.6 (1.3)		–0.1 (1.2)	
Range	–2.0 to 2.7		–4.0 to 2.0		–4.0 to 1.7		–3.7 to 1.7	
Improved ≥1 point on control score**	8	32	6	24	11	44	4	16
Difference, 95% CI (%)	8 (–17 to 33)				28 (4 to 52)			
Stayed within 1 point	9	36	14	56	9	36	15	60
Worsened by ≥1 point	8	32	5	20	5	20	6	24

*The mean of three distance control scores and the mean of three near control scores were analyzed. †Four of 25 prism group participants (16%) were assessed in trial frame (2 had not brought their spectacles to the visit, 1 had spectacles that did not contain prism, and 1 had spectacles with refractive error that was slightly off but within tolerances); 21 of 25 (86%) were tested in prism spectacles (1 should have been tested in trial frame because of incorrect refractive correction in spectacles). ‡Twenty-five of 25 nonprism group participants (100%) were assessed in study prescribed spectacles. §Difference in mean control (prism – nonprism) and 95% CIs are from the analysis of covariance model adjusting for corresponding baseline control score. ‖Change is 8 weeks minus baseline; thus, a negative value indicates improvement. Maximum range of change possible is –5 (improvement) points to 3 points (worsening) for distance control and –5 (improvement) to 5 points (worsening) for near control. **Control score improvement of ≥1 point between baseline and 8 weeks is the a priori definition of treatment response. CI = confidence interval; SD = standard deviation.

group, and 3.4 points at distance and 2.3 points at near in the prism group (Table 2).

Prism Spectacles and Spectacle Wear Adherence

In the prism group, the magnitude of base-in prism prescribed (mean, 10.4 ± 1.9Δ) was 6Δ for 1 participant (4%), 7Δ for 1 (4%), 8Δ for 2 (7%), 10Δ for 16 (57%), 12Δ for 5 (18%), and 14Δ for 3 (11%). Study spectacles were received at least 4 weeks before the outcome visit for 24 of 25 participants (96%) in each treatment group. Spectacle wear adherence in the prism group was deemed excellent in 22 participants (88%) and good in 3 (12%). Adherence in the nonprism group was judged excellent in 22 participants (88%), good in 2 (8%), and fair in 1 (4%).

Primary Outcome Visit Completion

The 8-week primary outcome visit was completed by 89% (25 of 28) of participants in both treatment groups. Forty percent (10 of 25) and 36% (9 of 25) of outcome visits were completed late

TABLE 4. Sensitivity analyses for 8-week distance control primary outcome

	n (%)		8-wk control score(mean)		Mean change from baseline		Adjusted difference
Sensitivity analyses	Prism	Nonprism	Prism	Nonprism	Prism	Nonprism	(prism – nonprism), mean (95% CI)
Limited to participants who received study spectacles at least 4 wk before the outcome visit	24 (96)	24 (96)	3.5	3.3	0.1	–0.2	0.3 (–0.5 to 1.1)
Limited to participants who were tested in study spectacles (not in trial frame)	21 (84)	25 (100)	3.6	3.3	0.0	–0.2	0.3 (–0.5 to 1.1)
Adjusting for baseline near control in addition to baseline distance control	25 (100)	25 (100)	3.6	3.3	0.1	–0.2	0.3 (–0.5 to 1.1)

CI = confidence interval.

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TABLE 5. Secondary outcomes at 8 weeks and change from baseline according to treatment group (N = 50)*

	Prism group†,‡ (n = 25)		Nonprism group (n = 25)	
Distance magnitude by PACT (Δ)				
At 8 wk				
Esodeviation	0	0%	0	0%
<10 Exodeviation	1	4%	0	0%
10–15 Exodeviation	0	0%	0	0%
16–18 Exodeviation	0	0%	5	20%
19–25 Exodeviation	3	12%	10	40%
26–35 Exodeviation	14	56%	9	36%
36–45 Exodeviation	6	24%	1	4%
>45 Exodeviation	1	4%	0	0%
Mean (SD)	30.6 (9.3)		26.5 (8.1)	
Range	1 to 47		16 to 45	
Change between baseline and 8 wk§				
Mean (SD)	5.3 (9.0)		1.1 (6.4)	
Range	–24 to 27		–10 to 12	
Near magnitude by PACT (Δ)§				
At 8 wk				
Esodeviation	0	0%	0	0%
<10 Exodeviation	1	4%	6	24%
10–15 Exodeviation	0	0%	3	12%
16–18 Exodeviation	1	4%	5	20%
19–25 Exodeviation	6	24%	4	16%
26–35 Exodeviation	15	60%	6	24%
36–45 Exodeviation	1	4%	1	4%
>45 Exodeviation	1	4%	0	0%
Mean (SD)	28.7 (8.2)		19.0 (9.8)	
Range	6 to 47		6 to 40	
Change between baseline and 8 wk				
Mean (SD)	7.0 (9.1)		–2.8 (9.1)	
Range	–14 to 27		–22 to 16	
Stereoacuity‖				
At 8 wk, arcseconds (log arcseconds)				
40 (1.6)	2	8%	9	36%
60 (1.78)	5	20%	4	16%
100 (2.0)	7	28%	7	28%
200 (2.3)	5	20%	2	8%
400 (2.6)	4	16%	1	4%
800 (2.9)	2	8%	2	8%
Mean (SD), log arcseconds	2.2 (0.4)		1.9 (0.4)	
Range	1.6 to 2.9		1.6 to 2.9	
Change between baseline and 8 wk				
Mean (SD)	–0.1 (0.5)		–0.2 (0.3)	
Range	–1.3 to 0.9		–1.2 to 0.3	
Suppression**				
Negligible (0)	1	4%	5	23%
Mild (1)	5	21%	3	14%
Moderate (2)	6	25%	4	18%
Dense (3)	12	50%	10	45%

*All values are unadjusted for baseline measures. †In the prism group, the PACT values are the sum of the in-prism PACT measurement plus the ground-in prism magnitude in the spectacles. ‡Lensometry indicated that the prism correction was accurate for 95% (21 of 22) of the prism-group participants who brought their spectacles to the outcome visit; one participant's spectacles did not contain any prism. §Adjusted treatment group difference (prism – nonprism) in mean exodeviation magnitude at 8 weeks is 4.1Δ (95% CI, –0.8 to 9.0Δ) at distance and 9.7Δ (95% CI, 4.5 to 14.9Δ) at near. Change in PACT is 8-week PACT minus baseline PACT; thus, a negative change indicates improvement. ‖Adjusted treatment group difference (prism – nonprism) in mean near stereoacuity at 8 weeks is 0.2 (95% CI, –0.01 to 0.4). Change in stereoacuity is calculated as 8 weeks minus baseline; thus, a negative change indicates an improvement. **The Office Suppression Test[19] is a three-step procedure to grade density of suppression in patients with intermittent exotropia who are manifestly exotropic. During an episode of manifest exotropia (spontaneous or induced), the participant viewed a 20/50 optotype at 6 m in normal room illumination and was asked whether one or two letters were seen. If two letters were reported, suppression was classified as "negligible" (grade of 0). If one letter was reported (indicating suppression), a single-point light source was viewed at 6 m with a red filter placed over the habitually fixing eye. If two lights were reported (one white and one red), suppression was classified as "mild" (grade 1). If one light was reported, the light source was viewed again in dim lighting with a red filter over the preferred eye. Suppression was classified as "moderate" (grade 2) if two lights were reported or dense (grade 3) if one light was reported. CI = confidence interval; PACT = prism-and-alternate-cover test; SD = standard deviation.

(between 10 and 24 weeks) in the prism and nonprism groups, respectively.

Primary Outcome

At the primary outcome visit, mean intermittent exotropia distance control was 3.6 points for the 25 prism group participants versus 3.3 points for the 25 nonprism group participants (adjusted difference, 0.3 points; 95% CI, –0.5 to 1.1; Table 3). Mean change in distance control from baseline to outcome was 0.1 point and –0.2 point in the prism versus nonprism groups. The three sensitivity analyses yielded similar results to the primary analysis (Table 4). Examiners reported being masked to treatment assignment for all outcome examinations.

Secondary Outcome for Distance Control

Treatment response (i.e., distance control improved ≥1 point from baseline) occurred in eight (32%) and six (24%) of those wearing prism spectacles and those not, respectively (treatment group difference, 8%; 95% CI, –17 to 33%; Table 3).

Additional Secondary Outcomes

At the primary outcome visit, the mean near control scores were 1.7 points for both the prism and nonprism groups (treatment

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TABLE 6. Child assessment of symptoms associated with intermittent exotropia at baseline and outcome

	Baseline				8-wk outcome*			
	Prism (n = 28)		Nonprism (n = 28)		Prism (n = 25)		Nonprism (n = 25)	
"In the past 2 weeks…" (baseline) "Since enrolling in the study…" (outcome)	n	%	n	%	n	%	n	%
Do your eyes hurt?								
Never	17	61	21	75	15	60	22	88
Sometimes	9	32	6	21	6	24	3	12
Almost always	2	7	1	4	4	16	0	0
Do your eyes feel funny?								
Never	16	57	21	75	17	68	20	80
Sometimes	10	36	6	21	7	28	3	12
Almost always	2	7	1	4	1	4	2	8
Do you have double vision (do you see two of things when you know there is really only one)?								
Never	10	36	20	71	17	68	17	68
Sometimes	12	43	6	21	8	32	7	28
Almost always	6	21	2	7	0	0	1	4
Is it hard for you to stare at things?								
Never	12	43	19	68	16	64	15	60
Sometimes	10	36	8	29	7	28	8	32
Almost always	6	21	1	4	2	8	2	8
Do you have problems with your eyes in the sun?								
Never	9	32	13	46	11	44	14	56
Sometimes	11	39	9	32	8	32	5	20
Almost always	8	29	6	21	6	24	6	24
Do your eyes go in and out?								
Never	16	57	19	68	20	80	19	76
Sometimes	10	36	7	25	2	8	3	12
Almost always	2	7	2	7	3	12	3	12
Is it hard to focus your eyes?								
Never	12	43	15	54	16	64	12	48
Sometimes	10	36	12	43	5	20	11	44
Almost always	6	21	1	4	4	16	2	8

*The Rasch-calibrated overall mean score on the Child IXT Symptom Questionnaire[18] at 8 weeks was 23.7 in the prism group versus 20.6 in the nonprism group (adjusted difference, –2.7; 95% confidence interval, –12.6 to 7.3).

group difference, 0.01; 95% CI, –0.7 to 0.7; Table 3). The proportion of participants whose near control improved ≥1 point from baseline was 44% (n = 11) and 16% (n = 4) of those wearing prism spectacles and those not, respectively (treatment group difference, 28%; 95% CI, 4 to 52%). The proportion of participants who did not have a spontaneous tropia during distance or near control testing was 21% (n = 6) in the prism group and 17% (n = 5) in the nonprism group (difference, 4%; 95% CI, –19 to 27%).

Mean total exodeviation magnitude by prism-and-alternate-cover test at the outcome visit was 30.6 versus 26.5Δ at distance (adjusted treatment group difference, 4.1Δ; 95% CI, –0.8 to 9.0Δ) and 28.7 versus 19Δ at near (adjusted group difference, 9.7Δ; 95% CI, 4.5 to 14.9Δ) in the prism and nonprism groups, respectively (Table 5). The mean increase in total exodeviation magnitude from baseline to outcome was 5.3 versus 1.1Δ at distance and 7.0 versus –2.8Δ at near, in the prism and nonprism groups, respectively (Table 5). Near stereoacuity and suppression data at outcome are found in Table 5.

In a post hoc analysis, full prism adaptation (increase in magnitude by at least the amount of prism worn) between baseline and outcome was found in 6 of 25 participants (24%; 95% CI, 9 to 45%) in the prism group.

Participant and Parent Questionnaires

Participant-reported intermittent exotropia-related symptoms and parent-reported symptoms possibly related to spectacle wear by treatment group at baseline and outcome are found in Tables 6 and 7, respectively. According to the parental and child questionnaires, none of

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TABLE 7. Parental survey: assessment of symptoms and spectacle wear issues at baseline and outcome

"In the past 2 weeks…" (baseline) / "Since enrolling in the study…" (outcome)	Baseline				8-wk outcome			
	Prism (n = 28)		Nonprism (n = 29)		Prism (n = 25)		Nonprism (n = 25)	
	n	%	n	%	n	%	n	%
Symptoms								
Has your child had headaches?								
Never	12	43	12	41	15	60	14	56
Almost never	8	29	10	34	8	32	6	24
Sometimes	8	29	6	21	2	8	5	20
Often	0	0	0	0	0	0	0	0
Almost always	0	0	1	3	0	0	0	0
Has your child had eyestrain (tired, sore, or uncomfortable eyes)?								
Never	8	29	7	24	16	64	11	44
Almost never	5	18	7	24	5	20	4	16
Sometimes	12	43	11	38	4	16	9	36
Often	3	11	3	10	0	0	1	4
Almost always	0	0	1	3	0	0	0	0
Has your child avoided reading or doing things up close?								
Never	18	64	16	55	22	88	15	60
Almost never	8	29	5	17	2	8	6	24
Sometimes	2	7	5	17	0	0	3	12
Often	0	0	3	10	1	4	1	4
Almost always	0	0	0	0	0	0	0	0
Has your child reported blurry vision?								
Never	13	46	20	69	21	84	21	84
Almost never	5	18	4	14	2	8	3	12
Sometimes	9	32	5	17	1	4	1	4
Often	1	4	0	0	1	4	0	0
Almost always	0	0	0	0	0	0	0	0
Spectacle wear problems								
Has your child looked over their spectacles?								
Never	7	25	5	17	12	48	14	56
Almost never	4	14	2	7	7	28	3	12
Sometimes	0	0	3	10	5	20	5	20
Often	0	0	0	0	0	0	3	12
Almost always	0	0	0	0	1	4	0	0
Never	17	61	19	66	0	0	0	0
Has your child taken their spectacles off when they should be wearing them?								
Never	7	25	3	10	5	20	10	40
Almost never	1	4	3	10	11	44	5	20
Sometimes	3	11	3	10	6	24	8	32
Often	0	0	1	3	3	12	1	4
Almost always	0	0	0	0	0	0	1	4
Not wearing spectacles	17	61	19	66	0	0	0	0
Has your child complained that the spectacles hurt their ears and/or nose?								
Never	9	32	4	14	17	68	14	56
Almost never	2	7	2	7	3	12	5	20
Sometimes	0	0	3	10	5	20	5	20
Often	0	0	1	3	0	0	1	4
Almost always	0	0	0	0	0	0	0	0
Not wearing spectacles	17	61	19	66	0	0	0	0

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the intermittent exotropia- or treatment-related symptoms seemed to worsen in the prism group between baseline and the primary outcome visit. At outcome, the mean Child Intermittent Exotropia Symptom Questionnaire score was 23.7 in the prism group versus 20.6 in the nonprism group (adjusted difference, –2.7; 95% CI, –12.6 to 7.3).

DISCUSSION

The results of this pilot randomized clinical trial of relieving base-in prism treatment using a magnitude equal to 40% of the larger exodeviation at distance or near for childhood intermittent exotropia did not meet our pre-determined criterion for proceeding to a full-scale randomized trial. The prism prescribing protocol used in our study did not yield better distance control than refractive correction alone, with our CI indicating that a 0.75-point-or-larger favorable effect of prism on distance control is unlikely.

Although base-in prism treatment is long recognized as a management option for intermittent exotropia, we could find only one small (n = 12) retrospective report of children who received base-in prism as their sole treatment modality.[21] However, full corrective rather than relieving prisms were prescribed in that study,[21] and there were numerous other differences in methodology precluding comparison with our study. In contrast to the present study evaluating relieving base-in prism treatment to facilitate normal sensorimotor fusion, most prior reports on base-in prism and intermittent exotropia have focused on whether a pre-operative prism adaptation test is useful in uncovering the maximum angle of exodeviation on which to base surgical dosage in the hope of improved surgical outcomes.[22–27] Generally, these studies defined prism adaptation as an increase in exodeviation of 5Δ (or 10Δ) or more after incrementally increasing the initial corrective prism magnitude for 30 minutes to 3 hours until no additional prism was required to neutralize the deviation. The frequency of prism adaptation using this method ranges from 8 to 100%,[22–28] with this phenomenon often interpreted to be similar to the uncovering of larger latent angles of exodeviation that are sometimes found with a monocular occlusion test.[23] It is unknown how the mechanisms underlying prism adaptation in intermittent exotropia might differ from those reported in patients with constant esotropia and anomalous retinal correspondence.[29–31] Further study of prism adaptation in patients with intermittent exotropia and other forms of strabismus is needed.

In evaluating for change in magnitude between baseline and 8 weeks in the present study, we found the prism group's mean exodeviation increased relative to the nonprism group at distance (+5.3 vs. +1.1Δ) and at near (+7 vs. –2.8Δ), with 24% of prism-group participants having shown full prism adaptation over this time, indicating that their distance and near angles at outcome exceeded their respective baseline angles by the amount of prism worn or greater. We do not know if the increase in angle was temporary or sustained because we did not remeasure the exodeviation after discontinuing prism wear. Prism adaptation (full or partial) during the study might be one reason why the prism treatment did not improve distance control outcomes or the mean near control outcome, although a significantly greater proportion (28%) of participants in the prism group showed ≥1 point improvement in near control from baseline.

In the present pilot study, we used a standardized prism magnitude of 40% of the larger of the distance or near exodeviation for all participants. Other clinical prism prescribing strategies, such as prescribing a larger magnitude or fully corrective prism[21,32] or prescribing the minimum prism power necessary to improve control of the exodeviation or to demonstrate better fusion on tests of suppression or stereoacuity,[7,9,20,33] may yield different results.

Our study has several important limitations. The study definition of full prism adaptation did not account for the wide test-retest repeatability for prism-and-alternate-cover test measurements in children with intermittent exotropia[34] and potential partial prism adaptation and for the true biological variability of intermittent exotropia magnitudes[35]; consequently, some participants might have had full or partial prism adaptation at enrollment. Prism-and-alternate-cover testing after prolonged monocular occlusion and through +3.00 D lenses at near was not completed at baseline, precluding determination of the maximum angle of exodeviation and classification of exotropia.[23] In addition, because this pilot study had a small convenience sample size, the analyses should be interpreted with caution. The sample size also precludes evaluating whether a relationship exists between prism adaptation and the depth of suppression. We did not determine whether anomalous retinal correspondence was present when the intermittent exotropia was manifest.

For future studies or use of other clinical prescribing strategies for base-in prism treatment for childhood intermittent exotropia, we suggest that an in-office prism adaptation test be performed using a broader definition of full prism adaptation that includes test-retest repeatability for the prism-and-alternate-cover test.[34] Clinicians and researchers should be aware that not only do a proportion of children with intermittent exotropia show immediate prism adaptation, but others adapt to prism over time, and thus, one should not only evaluate for short-term prism adaptation but also monitor for long-term prism adaptation.

In terms of the feasibility objective of conducting a randomized trial of base-in prism spectacles for children with intermittent exotropia, we found that recruitment was straightforward, outcome visit completion was reasonable despite the coronavirus 2019 pandemic, and examiners remained masked to treatment assignment. Any concerns by investigators that children would have difficulty wearing prism spectacles were unfounded because parent-reported adherence with prism spectacle wear of the magnitudes prescribed (6 to 14Δ) was excellent. Possible treatment-associated symptoms and issues with spectacles seemed similar between treatment groups. These aspects bode well for future studies that might evaluate different prism prescribing strategies for potential therapeutic effects and that might better identify and exclude children with prism adaptation.

CONCLUSIONS

Our a priori criterion for progressing to conduct a full-scale trial was not met. Base-in prism spectacles equal to 40% of the larger exodeviation (distance or near) worn for at least 8 weeks did not result in better distance control than nonprism spectacles in 3- to 12-year-old children with intermittent exotropia. Our findings suggest that a 0.75-point-or-larger favorable effect on distance control is unlikely with our prism prescribing protocol. It is unknown whether results might differ with other prism prescribing regimens or with different eligibility criteria. The phenomenon of prism adaptation in children with intermittent exotropia is worthy of further study.

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ARTICLE INFORMATION

Supplemental Digital Content: Appendix 1, available at http://links.lww.com/OPX/A607: Intermittent Exotropia Office Control Score.[3]

Appendix 2, available at http://links.lww.com/OPX/A608: Study Eligibility Criteria.

Appendix 3, available at http://links.lww.com/OPX/A609: Child Intermittent Exotropia Symptom Questionnaire[17,18] is a 7-item questionnaire that assesses intermittent-exotropia-related symptoms. The version for children 5 to <8 years is shown. The similar version for children 8 to 13 years has text-only responses and does not include the face pictures.

Appendix 4, available at http://links.lww.com/OPX/A610: Parent Spectacle Symptom Survey is a previously unpublished 7-item survey that asks parents about their child's intermittent exotropia-related symptoms and spectacle-wear issues.

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RJH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix 1. Intermittent Exotropia Office Control Score[14]

Control of exodeviation will be measured at distance and near using the Office Control Score.[14]

- Distance (6 meters) – fixing on an accommodative target such as a video or reading optotype letters
- Near (1/3 meter – fixing on Lang near-viewing stick or similar accommodative target)

The scale below applies to both distance and near separately.

<u>Intermittent Exotropia Control Scale</u>

5 = Constant Exotropia
4 = Exotropia > 50% of the 30-second period before dissociation
3 = Exotropia < 50% of the 30-second period before dissociation
2 = No exotropia unless dissociated, recovers in >5 seconds
1 = No exotropia unless dissociated, recovers in 1-5 seconds
0 = No exotropia unless dissociated, recovers in <1 second (phoria)
Not applicable = No exodeviation present

Directions:

Step 1: Assessment before any dissociation: Levels 5 to 3 are assessed during 30 seconds of observation; first at distance fixation and then at near fixation for another 30-second period. Both distance and near are assessed before any dissociation (i.e., before step 2, when assessing control scores of 0, 1, and 2). If the participant is spontaneously tropic (score 3, 4, or 5) at a specified test distance, then step 2 (assessment after standard dissociation) is skipped at that specific test distance.

Step 2: Assessment with standardized dissociation: If no exotropia is observed during step 1 (i.e., the 30-second period of observation at the specified test distance), levels 2 to 0 are then assessed as the worst of 3 rapidly successive trials of dissociation:

1. An occluder is placed over the right eye for 10 seconds and then removed, measuring the length of time it takes for fusion to become re-established.
2. The left eye is then occluded for 10 seconds (second assessment under dissociation), and the time to re-establish fusion is similarly measured.
3. The third assessment under dissociation is performed, covering the eye (for 10 seconds) that required the longest time to re-fuse.

The worse level of control observed following the three 10-second periods of occlusion should be recorded. Since the level under dissociation is recorded as the worst of the three assessments, if a score of 2 (>5 seconds recovery) is noted on the first or second dissociation, then subsequent dissociation(s) are not needed.

If the participant has a micro-esotropia by the cover test, but an exodeviation by the prism-and-alternate-cover test, the scale applies to the exodeviation.

Appendix 2. Eligibility Criteria.

Eligibility Criteria for Enrollment
1. Age 3 to < 13 years
2. Intermittent exotropia meeting all of the following criteria:
a. Intermittent exotropia or constant exotropia at distance
i. Mean distance control score of ≥2.0 points (mean of 3 assessments over the exam) and with at least one measure of 3, 4, or 5, (spontaneous tropia) during control testing
b. Intermittent exotropia or exophoria at near
i. Child cannot have a score of 5 points on all 3 near assessments of control
c. Distance exodeviation at least 16Δ measured by PACT and no larger than 35Δ
d. Near exodeviation at least 10Δ measured by PACT and no larger than 35Δ
e. Near deviation does not exceed the distance deviation by more than 10Δ by PACT (i.e., convergence insufficiency-type excluded)
3. Distance visual acuity (by any optotype method) in both eyes according to age normal values[15,16] as follows:
a. 20/50 or better for 3- to <4-year-olds
b. 20/40 or better for 4- to <5-year-olds
c. 20/32 or better for 5- to <7-year-olds
d. 20/25 or better for ≥7-year-olds
4. Interocular difference of distance visual acuity ≤ 2 lines (0.2 logMAR)
5. Refractive error between -6.00D SE and +2.50D SE (inclusive) (*based on a cycloplegic refraction performed within 7 months but prior to the day of enrollment*)
6. Refractive correction (pre-study spectacles) worn for at least 1 week if refractive error (*based on cycloplegic refraction performed within 7 months*) meets any of the following:
a. SE anisometropia ≥1.00D
b. Astigmatism ≥1.00D in either eye
c. SE myopia ≥-0.50D in either eye
7. If spectacles are worn, they must meet the following pre-enrollment criteria:
a. SE anisometropia corrected within <1.00D of full SE anisometropic difference
b. Astigmatism corrected within <1.00D of full magnitude; axis within 10 degrees if ≤1.00D of astigmatism and within 5 degrees if >1.00D of astigmatism
8. Gestational age ≥ 32 weeks
9. Birth weight >1500 grams
10. Parent understands the protocol and is willing to accept randomization to prism spectacles or non-prism spectacles
11. Parent has home phone (or access to phone) and is willing to be contacted by Jaeb Center staff and Investigator's site staff
12. Relocation outside of area of an active PEDIG site within next 8 weeks is not anticipated

Exclusion Criteria	
1.	Dissociated vertical deviation (DVD)
2.	Vertical deviation >3Δ in primary gaze at distance or near
3.	Pattern (such as an “A” or “V” pattern) with a downgaze measurement of >10Δ difference from straight ahead by PACT, measured by investigator’s routine method
4.	Treatment for IXT or amblyopia (other than refractive correction) within the past 4 weeks, including vision therapy, orthoptics, patching, atropine, or other penalization
5.	Substantial overminus spectacles (spectacles overminused by more than 1.00D SE than the most recent cycloplegic refraction and ALSO results in minus SE power in the spectacles; i.e. underplussing is allowed) within the past 4 weeks
6.	Prior strabismus, intraocular, or refractive surgery (including BOTOX injection)
7.	Prior use of prism spectacles
8.	Current contact lens wear
9.	Abnormality of the cornea, lens, or central retina
10.	Down syndrome or cerebral palsy
11.	Developmental delay which would, in the opinion of the investigator, interfere with treatment or evaluation. Mild speech delays, reading disability, and learning disabilities are not excluded.
12.	Any condition that would, in the investigator’s opinion, result in poor spectacle compliance
13.	Disease known to affect accommodation, vergence, or ocular motility such as multiple sclerosis, Graves orbitopathy, myasthenia gravis, diabetes mellitus, or Parkinson disease
14.	Current use of any ocular or systemic medication known to affect accommodation or vergence, such as anti-anxiety agents (e.g., Librium or Valium), anti-arrhythmic agents (e.g., Cifenline, Cibenzoline), anti-cholinergics (e.g., motion sickness patch (scopolamine)), bladder spasmolytic drugs (e.g., propiverine), hydroxychloroquine, chloroquine, phenothiazines (e.g., Compazine, Mellaril, Thorazine), tricyclic antidepressants (e.g., Elavil, Nortriptyline, Tofranil)
Additional Criteria for Randomization (Based on 30-minute In-office Prism Adaptation Testing)	
After 30 minutes of wearing 40% relieving prism in a trial frame, participants are eligible to be randomly assigned if all of the following are met:	
•	The participant has not fully adapted to prism at distance AND near
•	The participant’s PACT measurement at distance while wearing "trial” relieving prism is smaller than the originally measured deviation at distance OR near when not wearing prism (i.e., at least some reduction in deviation with prism)
•	The participant has no NEW near esotropia by cover test while wearing the “trial” relieving prism (e.g., a micro-esotropia previously noted on near cover test during initial testing and also noted at this time is allowed)
•	The participant has no esodeviation >6Δ on PACT at near while wearing “trial” relieving prism.

PACT = prism-and-alternate-cover test, Δ = prism diopter, DVD = dissociated vertical deviation, SE = spherical equivalent, D = diopter, IXT = intermittent exotropia, logMAR = logarithm of the minimum angle of resolution

Appendix 3. Child Intermittent Exotropia Symptom Questionnaire[17,18]

Instructions for Clinical Staff

Children should be positioned such that they are unable to view their parents during testing and parents should be advised not to influence their child's responses.

For each question, clinic staff will read the question and record the child's response on paper. Children can use the accompanying matching card or can respond verbally.

Each question should be answered. If the child does not appear to understand a question, clinic staff should repeat the question verbatim. Clinic staff should not try to explain the question or elaborate on the question, but should encourage children to choose the answer that best reflects how they feel.

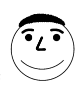
Before proceeding, clinic staff should read the following instructions aloud to the child and should present the sample question to determine whether the child understands the test. If the child does not understand the sample question, indicate that the survey and questionnaire will not be completed because the child does not understand the sample question.

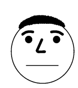
Instructions for Interviewer

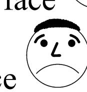
I am going to ask you some questions about some things that you might notice about your eyes. I would like to know how much you notice any of these things. There are no right or wrong answers. Choose the answer that is closest to how you feel.

If you are not sure how to answer, please choose the answer you think is best.

I am going to read each question and then you can point to the picture to show me how much you notice it.

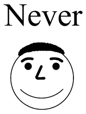
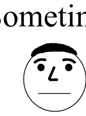
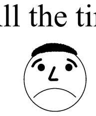
If you never notice it, point to the smiling face 

If you notice it sometimes, point to the middle face 

If you notice it all the time, point to the sad face 

Let's try a practice question:

Is it hard for you to ride a bike?

Never	Sometimes	All the time
		

1) Do your eyes hurt?

Never	Sometimes	All the time

2) Do your eyes feel funny?

Never	Sometimes	All the time

3) Do you have double vision (do you see two of things when you know there is really only one)?

Never	Sometimes	All the time

4) Is it hard for you to stare at things?

Never	Sometimes	All the time

5) Do you have problems with your eyes in the sun?

Never	Sometimes	All the time

6) Do your eyes go in and out?

Never	Sometimes	All the time

7) Is it hard to focus your eyes?

Never	Sometimes	All the time

Appendix 4. Parent Spectacle Symptom Survey

Instructions for Clinical Staff

The parent should complete the SPECTACLE SYMPTOM SURVEY by themselves on paper. If they are unable to complete this on their own, they may ask for assistance. Each question should be answered.

The symptom survey is a short survey about your observations of your child over the last two weeks. If you are unable to complete this on your own, please ask for someone to assist you.

1. Has your child had headaches?

Never	Almost never	Sometimes	Often	Almost always

2. Has your child had eyestrain (tired, sore, or uncomfortable eyes)?

Never	Almost never	Sometimes	Often	Almost always

3. Has your child avoided reading or doing things up close?

Never	Almost never	Sometimes	Often	Almost always

4. Has your child reported blurry vision?

Never	Almost never	Sometimes	Often	Almost always

5. Has your child looked over their spectacles?

Never	Almost never	Sometimes	Often	Almost always	Not wearing spectacles

6. Has your child taken their spectacles off when they should be wearing them?

Never	Almost never	Sometimes	Often	Almost always	Not wearing spectacles

7. Has your child complained that the spectacles hurt their ears and/or nose?

Never	Almost never	Sometimes	Often	Almost always	Not wearing spectacles

IXT7 – A Randomized Clinical Trial of Full-Time Alternate Patching Therapy for Intermittent Exotropia in Children.

Citation: Jenewein EC, Christiansen SP, Zhu Y, et al. A Randomized Clinical Trial of Full-Time Alternate Patching Therapy for Intermittent Exotropia in Children. Optom Vis Sci 2025 (accepted). Abstract previously presented at the American Academy of Optometry in 2025.

Jenewein EC, Christiansen SP, Zhu Y, et al. A Randomized Clinical Trial of Full-Time Alternate Patching Therapy for Intermittent Exotropia in Children. Optom Vis Sci 2025, accepted for publication.

Abstract:

Significance: Prescribed full-time alternate day patching was more effective than observation for improving distance control and magnitude of intermittent exotropia despite poor adherence. The duration of the treatment benefit observed and comparison to other treatment options requires further study.

Purpose: To determine whether 3 months of prescribed full-time alternate patching is more effective than observation for intermittent exotropia (IXT) in children.

Methods: We enrolled 73 children aged 3-<9 years with mean IXT distance control score (3 measures) ≥2 points (on a 0-5 [phoria constant tropia] scale) with at least one score ≥3, 4, or 5 (indicating spontaneous XT over 30-second observation) and a distance exodeviation of 15-50 prism diopters (Δ) by prism and alternate cover test (PACT), with the near deviation not exceeding the distance by >10Δ. Children were randomly assigned to 3 months full-time patching (all waking hours, 7 days/week, alternating eyes) or observation. The primary outcome was change in mean distance IXT control at 3 months.

Results: Baseline mean (SD) distance control for children assigned to full-time patching (N=36) and observation (N=37) were 3.6 (0.9) and 3.6 (0.9) points; mean distance PACT was 27Δ (9) and 27Δ (8), respectively. The 3-month visit was completed by 33 (92%) of 36 and 35 (95%) of 37 children assigned to full-time patching and observation. Mean patching adherence was 4.1 hours per day (95% CI: 2.8-5.5, N=20) by participants who returned temperature sensor occlusion dose monitors and 7.4 hours per day (95% CI: 5.8-8.9, N=33) by review of at-home calendars and interviews with parent and child. At 3 months, children in the patching group had greater improvement in mean distance control than the observation group: 0.9 (1.3) vs 0.2 (1.1) points (difference=0.62 points, 95% CI: 0.04 to 1.20, P=.04). There was also greater improvement in mean distance PACT: 6 (7) vs 2 (7) Δ, difference=4Δ (95% CI: 1 to 8, P=.02).

Conclusions: Three months of prescribed full-time alternate day patching improved distance control and magnitude of IXT in children 3-<9 years, despite mean adherence substantially less than the prescribed full-time regimen. Future studies should evaluate the durability of treatment effects and compare patching to other treatments.

IXT1 Surgical Dose Chart

Surgical Dose

The magnitude of deviation for which to perform surgery will be the largest preoperative deviation recorded at near, distance, or remote distance fixation by PACT. Data on this deviation will be entered on the Randomization Form. The recommended surgical doses are listed in Table 1 and Table 2, and will be generated as part of the randomization report. For recessions, the measurement of surgical dose should be made from the insertion of the muscle after muscle disinsertion. For resections, the measurement of surgical dose should be made from the insertion of the muscle prior to muscle disinsertion. Surgeons may adjust the surgical dose within 1.0 mm for each muscle at their discretion to account for individual patient variables, such as lateral incomitance and age.

Hangback, hemi-hangback, and adjustable techniques will not be allowed for this protocol, however, the surgeon may make epi-scleral tickbites at the intended insertion site and then bring the sutures forward to take a standard scleral bite at the original insertion site.

The target deviation, actual surgical dose, and any reasons for departure from the recommended dose tables will be recorded on the Surgery Form. Any complications during surgery will be recorded.

Table 1: Bilateral lateral rectus recession (BLRrec):

Angle of largest deviation	**Amount to recess each LR**
16 PD	4.0 mm
18 PD	5.0 mm
20 PD	5.0 mm
25 PD	6.0 mm
30 PD	7.0 mm
35 PD	7.5 mm
40 PD	8.0 mm

45 PD	8.5 mm
50 PD	9.0 mm

LR = lateral rectus

Table 2: Unilateral lateral rectus recession with medial rectus resection (R&R):

Angle of largest deviation	Amount to recess LR	Amount to resect MR
16 PD	4.0 mm	3.0 mm
18 PD	5.0 mm	4.0 mm
20 PD	5.0 mm	4.0 mm
25 PD	6.0 mm	5.0 mm
30 PD	7.0 mm	5.5 mm
35 PD	7.5 mm	6.0 mm
40 PD	8.0 mm	6.5 mm
45 PD	8.5 mm	6.5 mm
50 PD	9.0 mm	7.0 mm

LR = lateral rectus MR = medial rectus

INTERMITTENT EXOTROPIA 6 (IXT6) PROCEDURES MANUAL – Selections

Control of the Exodeviation

Control of the Exodeviation

Description
Method to assess the level of control of an exodeviation in participants with intermittent exotropia.

Procedure

Control of the exodeviation will be measured at distance and near using the Office Control Score (Mohney and Holmes, *Strabismus* 2006;14:147-150).

- Distance (6 meters ± 1 meter) fixing on an accommodative target such as a video for younger children or reading optotype letters for older children
- Near (1/3 meter – fixing on the hand-held fixation target – 20/30 equivalent single optotype column at 1/3 meter (Gulden Fixation Stick #15302)
- Testing of control must be performed by a pediatric ophthalmologist, pediatric optometrist, or a certified orthoptist.
- Testing must be done prior to dissociation or at least 10 minutes after any dissociation.

The scale below applies to both distance and near separately.

Intermittent Exotropia Control Scale
5 = Constant Exotropia
4 = Exotropia > 50% of the 30-second period before dissociation
3 = Exotropia < 50% of the 30-second period before dissociation
2 = No exotropia unless dissociated, recovers in >5 seconds
1 = No exotropia unless dissociated, recovers in 1-5 seconds
0 = No exotropia unless dissociated, recovers in <1 second (phoria)

Step1: Assessment before any dissociation: Eye alignment is observed for a 30-second period with distance fixation. The time in seconds that a spontaneous IXT is observed is counted, and the appropriate control score (3, 4, or 5) is assigned for distance fixation. This is then repeated for near fixation for another 30-second period; if an exotropia is observed, then the time in seconds that an eye is observed to be exotropic is counted and the appropriate score of 3, 4, or 5 is assigned. If a score of ≥3 is present, then Step 2 (dissociation) is not required for that test distance. First distance and then near fixation are assessed before any dissociation (i.e., before step 2).

Step 2: Assessment with standardized dissociation is performed only if spontaneous exotropia is NOT observed during step 1 (control was not a 3, 4, or 5). Instead, control will be a 0, 1, or 2; this is determined based on the worst score determined from 3 successive 10-second periods of dissociation:

- An occluder is placed over the right eye for 10 seconds and then removed; the length of time it takes for the re-establishment of fusion is measured in seconds.

- The left eye is then occluded for a 10-second period (second assessment under dissociation) and after uncovering the eye, the time for re-establishment of fusion is similarly measured in seconds.
- A third assessment is performed, by covering the eye that required the longer time to re-fuse on the first two 10-second dissociations. After uncovering the eye, the length of time it takes for the re-establishment of fusion is measured in seconds.

The worst level of control for the three 10-second periods of dissociation by occlusion should be recorded.

Since the control score is the slowest time of the three assessments, if a score of 2 (>5 seconds recovery) is noted on the first or second dissociation, then subsequent dissociation(s) are not needed.

Suppression Assessment

<u>Suppression Assessment</u>

Description

The suppression assessment is a standardized method of assessing the depth of suppression experienced while the participant is tropic (NOT aligned). Scoring is reported on an ordinal scale from 0 (no suppression) to 3 (dense suppression).

Required Equipment

- Fixation target at 6 meters (20/50 letter)
- Single point light source at 6 meters
- Opaque occluder
- Septum for dissociation (eg, flat object about the size of a half sheet of paper, such as a near card)
- Red filter
- Loose prisms

Procedure

<u>Pre-testing</u>:

- Demonstrate double versus single letter and double versus single light using printed cards.
- If unable to differentiate 1 versus 2 targets **do not proceed with testing** (outcome is recorded as "unable")
- Note that participant **must be tropic** when assessment of suppression status is made.
    - Cover one eye / use a septum to induce tropia if not already tropic
    - If unable to induce a tropia of sufficient duration to determine suppression status by briefly covering one eye or using a septum, introduce loose base-out prism of incrementally increasing magnitude in front of the typically deviating eye until tropic
        - Use the smallest magnitude necessary to induce tropia
        - Keep prism in place for testing
    - Perform cover/uncover test to confirm participant is tropic when reporting 1 letter/light

<u>Testing procedure</u>:
STEP 1

1. Ask the participant to fixate a single 20/50 optotype at distance
2. If not spontaneously tropic, cover one eye / use a septum / use base-out prism to induce a tropia
3. While tropic, ask the participant if they see 1 letter or 2
    - If 2 letters, record "negligible suppression" (score 0)

- If 1 letter, proceed to STEP 2

STEP 2

4. Ask the participant to fixate a single point light source at distance
5. If not spontaneously tropic, cover one eye / use a septum / use base-out prism to induce a tropia
6. Place the red filter over the fixing eye
   - If placing the red filter over the fixing eye causes a switch in fixation, simultaneously introduce the filter over the fixing eye and the occluder over the deviating eye
7. Cover 1 eye at a time to demonstrate that 1 eye sees a red light, 1 eye sees a white light
8. While tropic, ask the participant if they see 1 light or 2
   - If 2 lights, record "mild suppression" (score 1)
   - If 1 light, proceed to STEP 3

STEP 3

9. Dim room lights
10. Have the participant continue to fixate a single point light source at distance with the red filter over the fixing eye
11. If not already tropic, cover one eye / use a septum / use base-out prism to induce a tropia
12. While tropic, ask the participant if they see 1 light or 2
    - If 2 lights, record "moderate suppression" (score 2)
    - If 1 light, record "dense suppression" (score 3)

Suppression Test Flow Diagram

Citation:

Hatt SR, Leske DA, Holmes JM, et al. Testing depth of suppression in childhood intermittent exotropia. J AAPOS 2022; 26(1):36-38.e1.

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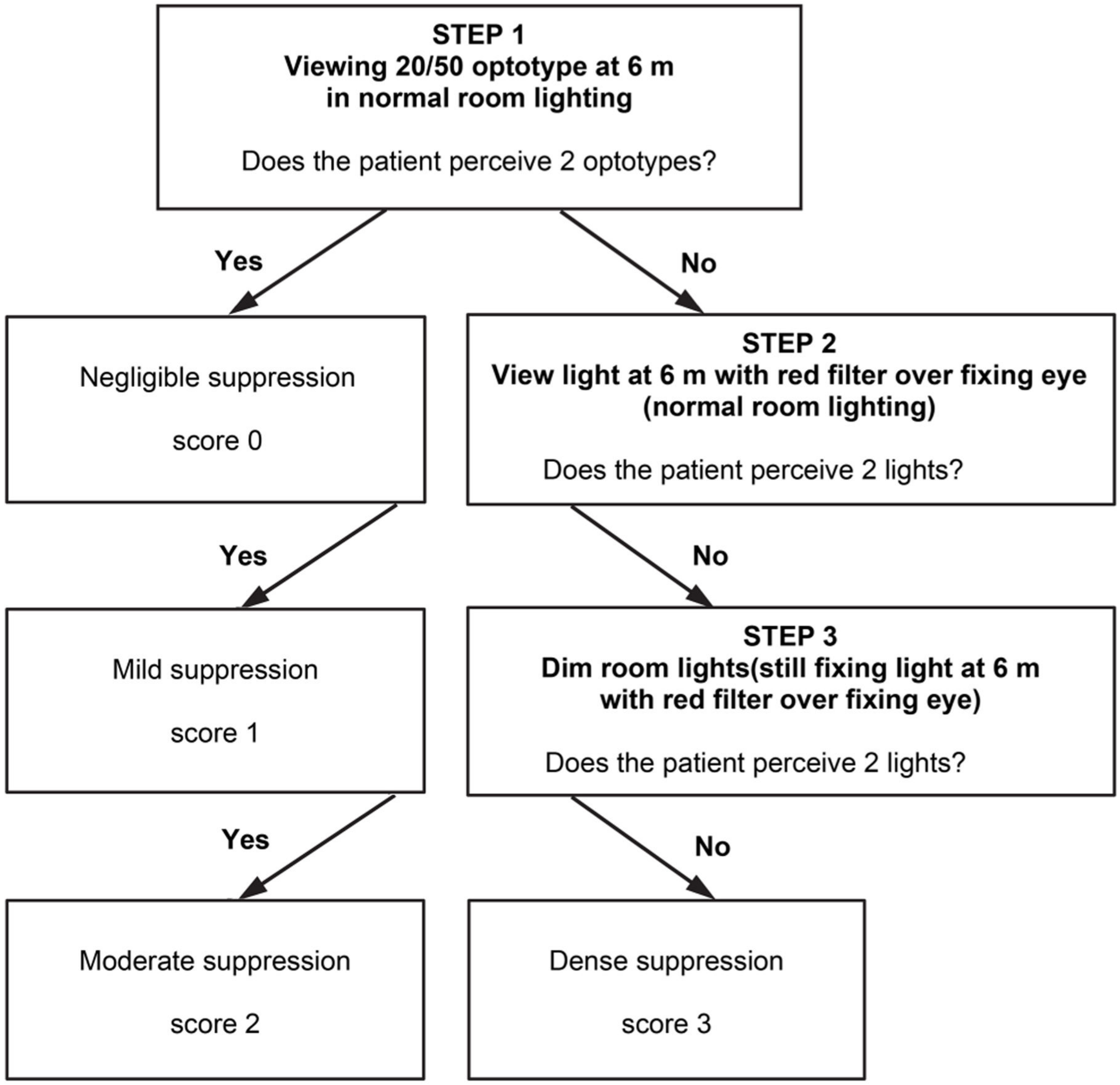

FIG 1.

Three steps of the Office Suppression Test procedure, grading suppression on a four-level scale (0, 1, 2, 3). All testing is to be performed while the exodeviation is manifest and the patient is fixing at 6 meters.

Ocular Alignment

Required Equipment

- Opaque (not translucent) occluder
- Loose plastic (not glass) prism set [increments 1/2, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 40, 45, 50 prism diopters (Δ)]
- Fixation targets at 1/3 meter (20/30 optotype on Gulden Fixation Stick #15302) and 6 meters (20/40 optotype)

Cover-Uncover Test

Description

The cover–uncover test is used to determine whether a tropia is present or not. The examiner is looking for re-fixational movements of one eye as the fellow eye is covered. If the unoccluded eye moves to take up fixation, a manifest deviation, or tropia, is present. If a tropia is present, the direction, frequency, and eye laterality are determined. The test is performed first at distance fixation using a 20/40 optotype and then at near fixation (1/3 meter) using a 20/30 letter accommodative target (on Gulden Fixation Stick #15302) (never a fixation light).

Procedure

1. Testing should be done with the participant wearing habitual refractive correction.
2. Ask the participant to read 20/40 letters (or name 20/40 pictures if unable to name letters) on a distant fixation target (6 meters).
3. Cover one eye with an opaque occluder for 2 to 3 seconds (long enough to allow for any re-fixational movements of the fellow eye).
4. As the cover is being placed over 1 eye, monitor the fellow eye for a refixation movement.
5. Remove the occluder so the participant may gain binocular fixation.
6. Repeat several times to rule out false-positives movements due to poor fixation or inattention.
7. Repeat steps 2-4 for the fellow eye.
8. Record whether a tropia was observed on the COVER portion or not.
9. Repeat entire procedure while the participant reads letters (or names pictures) on a 20/30 accommodative near target at 1/3 meter.

NOTE: If re-fixational movements of both the right and left eyes are observed, the tropia is defined as "alternating."

NOTE: Tropia is determined if re-fixation movement of the fellow eye is observed as an eye is being covered. Movement on uncover is not considered for this test.

Prism and Alternate Cover Test (PACT) Measurement

Description

The PACT is used to measure the full magnitude of a participant's ocular deviation, which includes any tropia plus any latent deviation. The PACT is performed at both distance (6 m) and near fixation (1/3 meter) using an accommodative target with letters that the participant can read (or pictures the participant can name, but never a fixation light). Plastic loose prisms should be held in the frontal plane position.

Procedure
1. Place a single appropriately oriented prism in the frontal plane position before the glasses lens of one eye (or before the eye if glasses are not required for testing).
2. Alternately occlude one eye at a time with a cover paddle, pausing for 1-2 seconds over each eye, then moving quickly from one to the other without allowing binocular viewing at any point.
3. Observe the re-fixation movement of the just-uncovered eye.
4. Incrementally increase the prism amount until reversal of the movement of the deviating eye is seen.
5. Record the magnitude of prism that is closest to producing no movement (neutral).
6. Record the direction of the deviation.

AC/A Ratio Determination

Description
The AC/A ration is determined by measuring the angle of deviation using the PACT while increasing the accommodative demand and comparing this angle of deviation to the deviation measured by PACT in habitual correction.

Required Equipment
- Halberg clips or trial frame
- -2.00D lenses

Procedure
1. Place -2.00D lenses over the habitual correction using Halberg clips if wearing spectacles or using trial frames if not wearing spectacles.
2. With the participant wearing the -2.00D lenses, repeat the PACT measurement at 6 meters and record the value.
3. The AC/A ratio is calculated automatically by the website by dividing the difference of the distance PACT measurements with and without the -2.00D lenses by 2.

Fusional Amplitude Testing

Fusional Amplitude Testing

Description
Fusional amplitudes are a measure of how well a participant can converge their eyes using fusional vergence. It is measured by increasing base-out prism to the point that the participant is no longer able to control the deviation. The total amount of fusion is the magnitude of the base-out prism the participant was able to overcome plus the magnitude of the deviation.

Required Equipment
- Horizontal prism bar (Gulden B-16 EZ View: increments 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, and 45 prism diopters)
- Hand-held fixation target – 20/30 equivalent single optotype column at 40 cm (Gulden Fixation Stick #15302)

Procedure
1. Ensure good illumination using ambient and overhead lighting.
2. Testing should be done with the participant wearing habitual refractive correction.
3. Hold the target 40 cm in front of the participant at eye level.
4. Instruct the participant to "try to keep the target single and clear as long as possible" as base-out prism is slowly introduced before one eye.
5. Ask the participant at each prism level if the target is single and clear.
6. Ask the participant to report when they experience blurred or double vision or if the target starts to move sideways.
7. Then increase the amount of base-out prism in front of the right eye at approximately 1 prism bar increment every 2 seconds until 20Δ, followed by 1 prism bar increment every 5 seconds after 20Δ, stopping when the participant reports that the target blurs, moves laterally, or doubles.
8. If the participant reports blur, ask the participant "can you make it clear or does it stay blurry?" If it stays blurry, note the prism increment where this was reported as this will be recorded as the "blur," but continue increasing the base-out prism as you ask the participant to now tell you when it breaks into 2.
9. If the target becomes double, ask the participant "can you make it 1 or does it stay 2?" If the participant reports that the target is now 1, increase the prism amount until diplopia is reported. When the participant can no longer keep the target single, record this value as the base-out break.
10. If you note that a break in fusion has occurred and the participant does not report diplopia (the participant may then be suppressing), record this value as the base-out break.
11. After the participant reports double vision or you see a break in fusion, add 1 more prism-bar increment of base-out prism.
12. Ask the participant to report when they can get the target back together into one.

13. Then reduce the base-out prism at a rate of about 1 prism bar increment every 5 sec until 20Δ is reached, followed by 1 prism bar increment every 2 seconds for prism increments < 20Δ until the participant regains single vision.
14. Complete the full sequence and then record the blur, break, and recovery findings.
15. If blur does not occur, you will record an "X" for the blur finding.

NOTE: If diplopia is not reported, but the examiner notes a loss of fusion, the prism through which fusion is lost will be recorded as the "break" finding. Likewise, an examiner's observation of recovery of fusion will be recorded as "recovery."

NOTE: If the participant is able to fuse the largest (45Δ) prism, record 50Δ for the break value and have the participant close or cover one eye to break fusion so that recovery can be measured. Record the amount of prism through which the participant was able to regain fusion (maximum value would be 45Δ).

NOTE: *When testing for recovery, if the participant does not achieve single vision even with no prism in place, add base-in prism until fusion occurs and record the values as "minus" (i.e. -8)*

NOTE: *If diplopia is reported initially (without introducing prism), record zero for both the break point and recovery values, and mark 'X' for the blur point.*

Stereoacuity

Randot Preschool Stereotest

Description
The Randot Preschool Stereotest measures random dot stereoacuity from 800 to 40 arc seconds (800”, 400”, 200”, 100”, 60”, 40”).

The Randot Preschool Stereotest consists of 3 booklets (or 3 tests within 1 booklet for newer versions of the test) with random dot shapes which can be matched to non-stereo shapes on the opposing page. There are a total of six levels (seconds of arc), with two levels in each book/test. Each level has 4 rectangles, 3 that contain shapes and one that is blank.

Required Equipment
- Preschool Randot Test (Books/Tests 1, 2, and 3)
- Polarized glasses

Specifications
- Testing order is Book/Test 3 (800”/400”), Book/Test 1 (200”/100”), Book/Test 2 (60”/40”).

Procedure
1. Testing should be done with the participant wearing refractive correction.
2. As a pretest, use Book/Test #3 (800”/400”).
3. Point to the top 4 panels of non-stereo side (black on white shapes) and ask, “Can you point to the duck?” If the child cannot correctly identify the duck, do not proceed with the rest of the test.
4. Starting with Book/Test 3, turn to the Randot side of the test booklet starting with the top level and point to one of the boxes containing a Randot shape, asking the participant what shape is in the box. The child should be encouraged to match one of the black and white shapes to the Randot shape.
5. Continue by pointing to another shape at the same level.
6. If 2 shapes are identified correctly at a level, testing will proceed to the next level.
7. If 2 shapes are identified incorrectly at a level, testing will stop at the current level.
8. The final score will be calculated as the finest level (lowest seconds of arc measured) at which 2 shapes were correctly identified.
9. If 0 or only 1 shape are correctly identified at the 800” level but the pretest question was answered correctly, record “nil” as the score.

Testing must be completed by a PEDIG certified Stereoacuity examiner.

An instructional video for certifying administration of the Randot Preschool Stereotest is available on the PEDIG website, filed under Certification Materials > Stereoacuity Testing Certification.

http://publicfiles.jaeb.org/pedig/videos/RandotVideo.avi