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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

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.

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

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.

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

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

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.

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 ≥10Δ 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

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

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.

Acknowledgments

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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).

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)

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)

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)

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

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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)

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)

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Boston MA – Tufts Medical Center (2)

Mitchell B. Strominger, (I); Shelley J. Klein, (C); Noopur N. Batra, (C); Vicki M. Chen, (E); Jenelle L. Mallios, (E)

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Andrew J. Levada, (I); Tara H. Cronin, (I); Nathalie M. Gintowt, (C); Susan H. Heaton, (C); Cheryl Capobianco, (E)

Indianapolis IN – Indiana University School of Medicine (1)

Daniel E. Neely, (I); Michele E. Whitaker, (C); Jingyun Wang, (C); Dana L. Donaldson, (E); Jay G. Galli, (E)

Grand Rapids MI – Pediatric Ophthalmology, PC (1)

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Sharon MA – Daniel M. Laby, M.D. (1)

Daniel M. Laby, (I); Beth G. Harper, (E)

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Jonathan M. Holmes (Planning Committee Chair), Sean P. Donahue (Protocol Chair, Intermittent Exotropia Study 1), Susan A. Cotter (Protocol Co-Chair, Intermittent Exotropia Study 2), Brian G. Mohney (Protocol Co-Chair, Intermittent Exotropia Study 2), Roy W. Beck, Eileen E. Birch, Danielle L. Chandler, Stephen P. Christiansen, Sarah R. Hatt, Raymond T. Kraker, David A. Leske, Michele Melia**,** Mary O'Hara, Yi Pang, Michael X. Repka, Kenneth Romanchuck, Susanna M. Tamkins, David K. Wallace, David T. Wheeler

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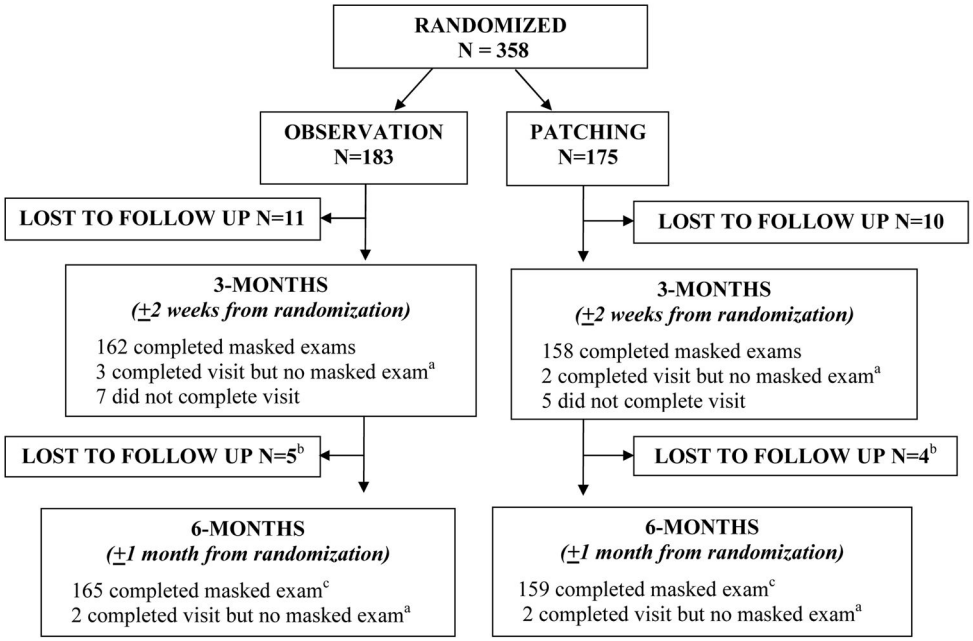
Marie Diener-West (Chair), John D. Baker, Barry Davis, Donald F. Everett, Dale L. Phelps, Stephen Poff, Richard A. Saunders, Lawrence Tychsen



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.

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

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)

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

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

	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

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

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