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One-Year Strabismus Outcomes in the Infant Aphakia Treatment Study

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Abstract

Objective—To evaluate the characteristics of strabismus in infants who underwent cataract surgery with and without intraocular lens (IOL) implantation.

Design—Secondary outcome analysis in a prospective, randomized clinical trial

Participants—The Infant Aphakia Treatment Study (IATS) is a randomized, multicenter (n = 12) clinical trial comparing treatment of aphakia with a primary IOL or contact lens in 114 infants with a unilateral congenital cataract.

Intervention—Infants underwent cataract surgery with or without placement of an IOL.

Main Outcome Measures—The proportion of patients who developed strabismus during the first 12 months of follow-up was calculated using the life-table method, and compared across treatment groups and age strata using a log-rank test.

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¹⁰Appendix 1

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Results—Strabismus developed within the first 12 months of follow-up in 38 (life table estimate: 66.7%) pseudophakic infants and 42 (life table estimate: 74.5%) infants treated with contact lenses ($p=0.59$). The younger cohort (< 49 days) at the time of surgery developed less strabismus (29 of 50, life table estimate: 58.0%) than the older cohort (≥ 49 days) (51 of 64, life table estimate: 80.0%) ($p<0.01$).

Conclusions—Intraocular lens placement does not prevent the early development of strabismus following congenital cataract surgery. However, strabismus was less likely to develop in infants whose cataract was removed at an earlier age.

Introduction

Strabismus is a common finding in infants with unilateral congenital cataract, with a reported frequency ranging from 27 to 100%.^{1–10} Prior reports have suggested that strabismus develops less frequently when an intraocular lens (IOL) is implanted primarily.^{1,2} Such reports are limited by retrospective design and small sample size.

The Infant Aphakia Treatment Study (IATS) is a multicenter, randomized, controlled clinical trial sponsored by the National Eye Institute. The aim of IATS is to compare the visual outcomes and complications of the correction of aphakia using a contact lens to those when an IOL is placed primarily after monocular cataract surgery in infants aged 1 to 6 months. The primary outcomes at one year after cataract surgery including visual acuity, adverse events, and additional surgeries have been previously described.¹¹ In this report we compare the timing of onset and characteristics of strabismus between the two treatment cohorts up to one year postoperatively.

Materials and Methods

The IATS study group, design and clinical measures at enrollment have been previously described and therefore are only briefly summarized in this report.¹² The complete protocol for the IATS can be viewed online (<http://www.sph.emory.edu/IATS>, 10/21/2009). This study was approved by the institutional review boards of all the participating institutions and was in compliance with the Health Insurance Portability and Accountability Act. An investigational device exemption (# G020021) was obtained for the off-label research use of the Acrysof SN60AT and MA60AC IOLs (Alcon Laboratories, Fort Worth, Texas).

Study Design

The main inclusion criteria were a visually significant congenital cataract (≥ 3 mm central opacity) in one eye and an age of 28 days to <210 days at the time of cataract surgery. Patients with a unilateral cataract associated with any degree of persistence of the fetal vasculature (PFV) were allowed in the study as long as the PFV was not associated with visible stretching of the ciliary processes or involvement of the retina or optic nerve as determined by the treating IATS investigator. The other main exclusion criteria were an acquired cataract, a corneal diameter <9 mm, and prematurity (<36 gestational weeks). Patients were randomized to either have an IOL placed at the time of the initial surgery (with spectacle correction of residual hyperopia) or to be left aphakic (with contact lens

correction). The randomization was stratified according to the category of the age of the infant at surgery (28 – 48 days versus 49 – 210 days.).

Examination Methods

Patients were examined at baseline and 1 day, 1 week, and 1, 3, 6, 9 and 12 months after surgery. Acuity, refractive error, and ocular alignment testing were assessed at each follow-up examination by an IATS-certified investigator. Strabismus was assessed at all postoperative follow-up visits starting at the 1 month visit. Monocular grating acuity was measured at one year of age (± 2 months) by a traveling examiner (Teller Acuity Cards; Stereo Optical Company, Chicago, Illinois). The cycles/cm of the card with the highest spatial frequency to which the child showed a clear response was transformed to a logMAR scale, the logarithm of the minimum angle of resolution, for analysis and reporting. The infant's optical correction was updated regularly based on retinoscopic findings to a target refraction of -2.00 D sphere. All caregivers were instructed on how to patch their infants according to the study protocol. Manifest strabismus at 33 cm was estimated by Hirschberg or measured in prism diopters (PD) by Krinsky light reflex testing or the prism-alternate cover test and simultaneous prism cover test when feasible. Intermittency and control of ocular misalignment was not a required recording.

Analysis Methods

The proportion of patients (in percent) with strabismus at baseline was compared between the treatment groups and age strata using a chi-square test. The development of strabismus was evaluated using two different approaches: the cumulative development of strabismus over time and its prevalence at the 12-month postoperative visit.

The cumulative percentage of patients developing strabismus over study visits during the first 12 months after surgery was calculated using a life table method, since follow-up through 12 months was not available for all patients. The last visit within the first 12 months after surgery was at 9 months for 8 patients and at 3 months for 1 patient. The first visit at which strabismus was noted was considered the onset of strabismus, even if some prior visits had been missed. A patient was censored at the last available visit during the first 12 months after surgery at which they were found not to have strabismus. This approach provided an estimate of the cumulative percentage of patients having strabismus at each of the follow-up visits during the first 12 months after cataract surgery; the percentages were compared between treatment groups as well as between age strata using a log-rank test. If a visit was missed or strabismus was not measured at a visit, it was assumed that the strabismus status of the patient had not changed. At baseline, strabismus was not measured in six patients and we assumed they were orthotropic. During follow-up, the number of visits that were missed or at which strabismus was not measured were: 1 visit for 9 patients, 2 visits for 1 patient, and 3 visits for 1 patient.

The percentage of patients with strabismus at the visit 12 months after surgery was also determined. For those patients that had strabismus surgery prior to the 12 month post-operative visit, the alignment at the time of surgery was utilized. The percentages of patients

with strabismus at the 12 months postoperative visit were compared between treatment groups and age strata using a chi-square test.

The association of strabismus and visual acuity was evaluated using the measure of strabismus at the clinic exam done closest to the time at which the monocular grating acuity was measured by a traveling examiner. The median visual acuity at 1 year after surgery was compared between patients with and without strabismus using the Wilcoxon rank-sum test. A nonparametric test was used because of the skewed distribution of visual acuity and because of the assignment of visual acuity values for patients with vision below the level detectable with Teller Acuity Cards.¹

When describing the alignment angles, patients with a combination of horizontal and vertical strabismus were grouped according to the horizontal deviation. All statistical tests were 2-sided. No adjustment was made for multiple testing. $P < .05$ was deemed statistically significant.

Results

Study Population and Prevalence of Strabismus at Baseline

One hundred fourteen infants were enrolled in the study from December 23, 2004, through January 16, 2009. Fifty-seven patients were randomized to each treatment group. The median age at cataract surgery was 1.8 months (inter-quartile range = 1.1 – 3.2 months), 60 (52.6%) patients were female, and 97 (85.1%) patients were white.

At enrollment, 28 (24.6%) of the 114 infants had strabismus. Esotropia was present in 12 (42.9%) of the patients with strabismus, with angles ranging from 15 to 40 Prism Diopters (PD) in the 8 patients in whom the magnitude of the deviation was recorded. Exotropia was present in 16 (57.1%) of the patient with strabismus with angles ranging from 15 to 75 PD in 11 of the 16. One subject with esotropia also had a hyperdeviation of 5 PD. The prevalence of strabismus at baseline did not differ between the treatment groups (contact lens: 16 patients (28.1%), IOL: 12 patients (21.1%), $p = 0.38$). Patients who underwent cataract surgery at a younger age were less likely to have strabismus. Among 50 patients in the younger cohort (28 to 48 days) 3 patients (6.0%) had strabismus compared with 25 (39.1%) of the 64 patients in the older cohort (49 to 210 days) ($p = 0.0006$).

Longitudinal Development of Strabismus

The percentage of patients developing strabismus over time increased from 24.6% at baseline to 70.4% by 12 months after cataract surgery (Figure 1). The pattern of the development of strabismus over time did not differ between the treatment groups ($p = 0.59$) with estimates at 12 months of 66.7% among the pseudophakic infants and 74.5% among the infants treated with contact lenses. The development of strabismus over time depended on the age at cataract surgery ($p = 0.0006$, Fig. 2) with estimates at 12 months of 58.0% for the younger cohort and 80.0% for the older cohort. Of 74 patients with strabismus at some point after cataract surgery, 70 (94.6%) had an angle of deviation greater than 8 PD on at least 1 visit.

The cumulative development of strabismus for infants who did not have strabismus at baseline (n=86) was also calculated. Strabismus developed within 12 months of surgery in 60.7% of patients (57.8% of the pseudophakic infants (n=45) and 64.6% of those treated with contact lenses (n=41) (p=0.97)). When subdivided into age groups, the percentage of patients developing strabismus during the first 12 postoperative months was not different between the younger cohort (55.3%, n=47) and the older cohort (67.1%, n=39) (p=0.19). Of the 27 patients with strabismus at baseline and followed for 9–12 months after surgery, 5 (18.5%) (2 in the younger age group and 3 in the older age group) were orthotropic at 1 month and stayed orthotropic for the remainder of follow-up and 7 (25.9%) went on to have strabismus surgery before 12 months after surgery.

Prevalence of Strabismus at 12 months after Cataract Surgery

Of the 105 patients for whom a 12-month ocular alignment data was available, 54 (51.4%) had strabismus. Fifteen (14.3%) underwent strabismus surgery prior to that visit, thus necessitating the use of their preoperative angle for the 12-month analysis. Among patients in the contact lens group, 31/53 (58.5%) had strabismus compared with 23/52 (44.2%) patients in the IOL group (p=0.14). Esotropia was present in 25 (47.2%) of patients in the contact lens group and 12 (23.1%) of patients in the IOL group. Exotropia was present in 6 (11.3%) of patients in the contact lens group and 10 (19.2%) of patients in the IOL group. One patient (1.9%) in the IOL group had hypertropia. When subdivided by age category, the younger cohort had less strabismus, 15 of 46 (32.6%), than the older cohort, 39 of 59 (66.1%) over 12 months (p= 0.0007). It has been reported that 58 of the 114 IATS patients (50.9%) developed an adverse event (AE) in the first year following cataract surgery.¹¹ Among the patients with one or more adverse event, 30/48 (63%) had strabismus compared with 22/38 (58%) in the patients without an adverse event (p=0.82).

Strabismus and Visual Acuity at 1 Year of Age

The association of strabismus with visual acuity in the treated eye at 1 year of age was based on the measurement of strabismus taken at the clinic visit closest to the time of the visual acuity assessment. At that time, 12 of the patients had undergone strabismus surgery. Of the 114 patients 71 (62.3%) were orthotropic and 43 (37.7%) had strabismus. There was a trend for better visual acuity at 1 year of age in the treated eye in patients without strabismus (strabismus median visual acuity, 0.97 logMAR (interquartile range = 0.80 – 1.67), no strabismus median visual acuity, 0.80 (interquartile range = 0.66 – 0.97); p=0.06, Figure 3). No such trend was seen when excluding the 12 patients who had strabismus repair (strabismus (n=34): median visual acuity, 0.88 logMAR (interquartile range = 0.80 – 1.27), no strabismus (n=68): median visual acuity, 0.80 logMAR (interquartile range = 0.66 – 0.97); p=0.20) or when excluding the 28 patients with strabismus at baseline, (strabismus (n=29): median visual acuity, 0.80 logMAR (interquartile range = 0.80 – 1.54), no strabismus (n=57): median visual acuity, 0.80 (interquartile range = 0.66 – 0.97); p=0.35).

Strabismus Surgery

Fifteen patients (13.2%) underwent strabismus surgery in the 12 months following surgery, with near strabismus angles ranging from 20 – 66 PD of esotropia or exotropia. Their postoperative alignment ranged from orthophoria (5 patients (33.0%) to 20 PD esotropia at

the next study visit; 8 of the 15 (53.3%) were within 8 PD of orthophoria at a median follow-up of 62 days (range = 4 – 99days) after strabismus surgery.

Discussion

In the first year of this randomized clinical trial the development of strabismus does not differ when monocular congenital cataracts are managed with either a contact lens or an IOL. This was true for the cumulative percentage of patients with strabismus at any exam during the first 12 months after surgery and the percentage of cases who had strabismus at the 12 month visit. The prevalence of strabismus prior to surgery was 24.6% and by 12 months after surgery had risen to 70.4%, which conforms with previous reports of strabismus in the setting of monocular congenital cataracts.^{1–10} Other studies have shown occurrence rates from 55% to 100%.^{2,5} In IATS, the development of strabismus was not affected by the occurrence of an adverse event.

Various reports have suggested a difference in the frequency of development of strabismus depending on whether aphakia was treated with an IOL or contact lens. Lambert et al described rates of strabismus of 92% using contact lenses and 75% using IOLs in a non-randomized cohort of 25 infants after unilateral cataract surgery, but this difference was not statistically significant.¹ Autrata et al reported a similar benefit in reduction of strabismus rates for infants who received an intraocular lens (55% strabismic) compared to those using a contact lens (83% strabismic).² In the IATS, a slightly lower rate of strabismus was found in the IOL group either cumulatively or at 12 months postoperatively), however the difference was not statistically significant.

Esotropia was the most common strabismus pattern in both treatment arms. This is consistent with previous reports of similar patients (Spanou 76.5%, Parks and Hiles 66%, Cheng 59%, Lambert 50%),^{1,3,5,13,14} In our study, esotropia occurred more frequently in the contact lens group. Vertical deviations were uncommon (1.9%) at 12 months postoperatively.

Strabismus surgery was performed and dosed per surgeon discretion and improved the ocular alignment in 15 patients (53.3% within 8 PD of orthotropia). Others have found a higher success rate for strabismus surgery with pediatric pseudophakia. Weisber et al, Hiles and Sheridan, and Merino reported success rates between 75 and 83.3% in older children.^{9,15,16}

Strabismus was less common in the group of infants who had surgery before 49 days of age. Since the most critical period for development of stereopsis is in the first months of life, this result is not surprising.¹⁷ It is understood that suppression from a dense cataract in an infant impacts not only the development of vision, but also binocularity. Thus removing a cataract at an earlier age may facilitate binocularity and maintenance of orthophoria. Since others have found higher rates of strabismus in the setting of monocular aphakia in infancy,^{14,18} the improved alignment in our youngest patients is encouraging.

At one year of age, it appeared that patients without strabismus trended to have better acuity than those with strabismus. However this trend dissolved when either the patients who had

strabismus surgery or those with strabismus at baseline were excluded. Thus it is not known whether better acuity in the treated eye is protective for the development of strabismus or whether straighter alignment improves amblyopia treatment after cataract surgery. Further follow up is needed to identify any possible relationship between ocular alignment and vision or clinical course.

The largest limitation of this study is that long term follow up is not available regarding this secondary outcome in the IATS cohort. Other limitations include the fact that 11 patients did not have complete follow-up data and that strabismus surgery was performed in 15 patients within the first year after cataract surgery. There is also the issue of statistical power for this post-hoc analysis of a secondary outcome. With 57 patients per group and with 70% of patients overall having strabismus by one year after surgery, the true difference between the treatments would have to be 24% (82% versus 58%) for this analysis to have 80% power to detect a difference between the treatment groups with an alpha of 0.05.

In conclusion, at 12 months after surgery, the type of aphakia management does not appear to significantly influence the rate of strabismus development. Strabismus occurred more frequently in infants whose cataracts were removed at an older age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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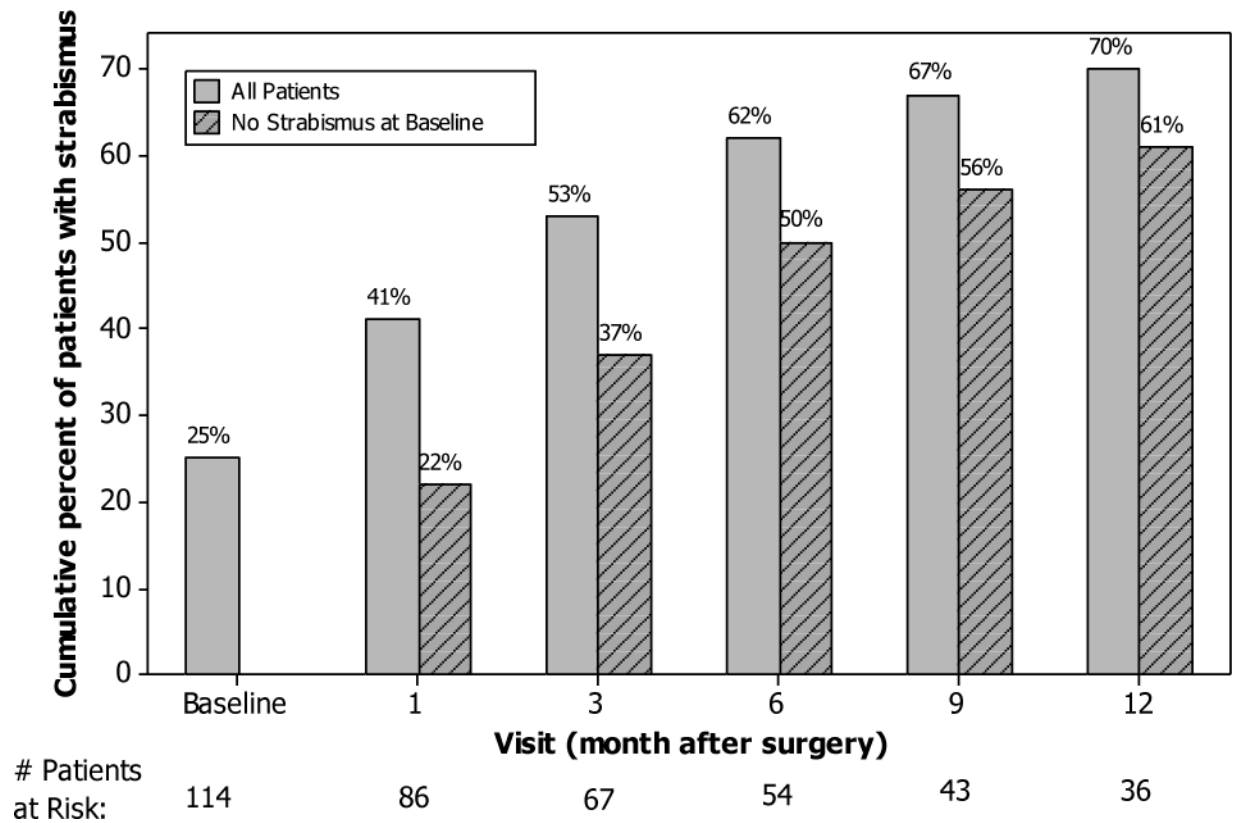


Figure 1.

Life-table estimates of the cumulative percent of patients demonstrating strabismus over time for all patients and for those without strabismus at baseline.

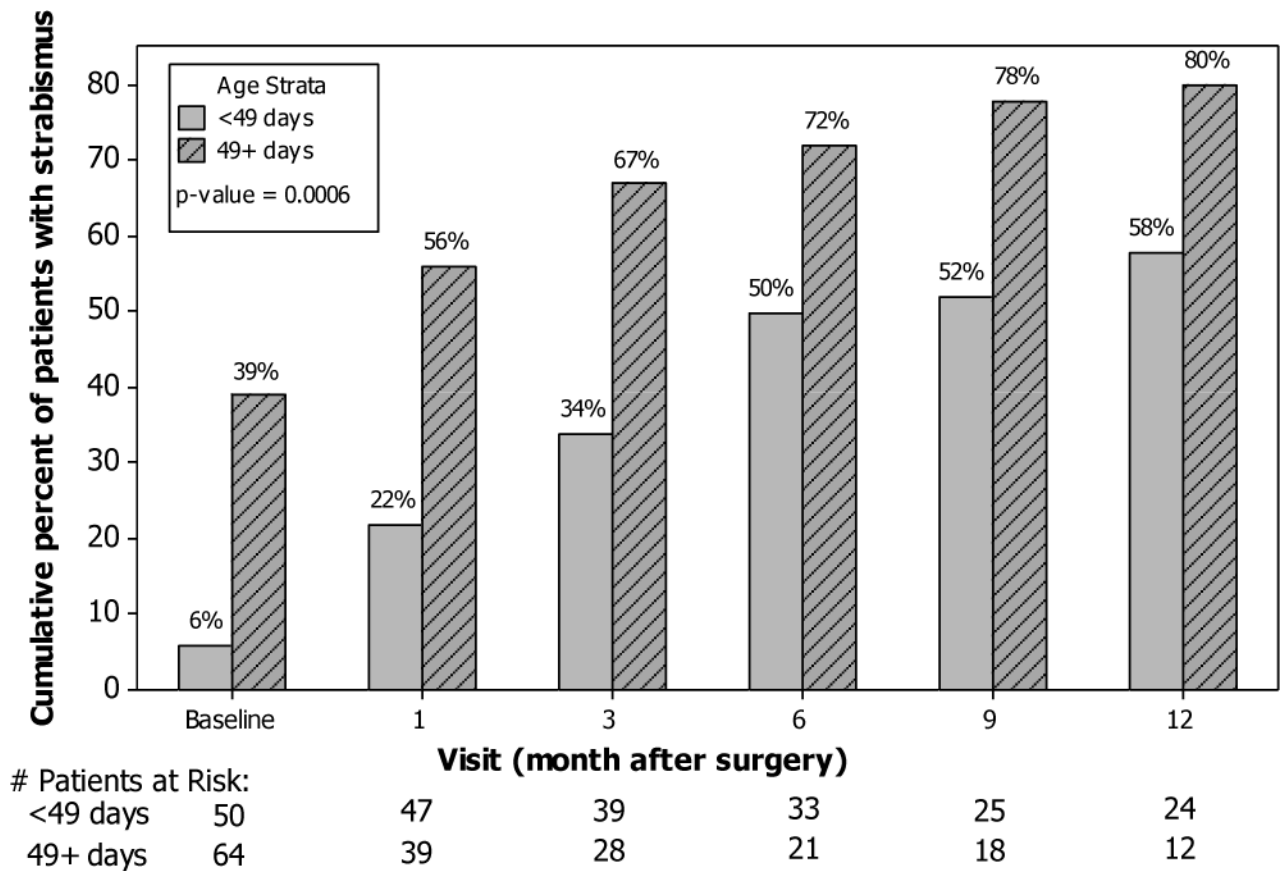


Figure 2.

Life-table estimates of the cumulative percent of patients demonstrating strabismus over time according to age at the time of cataract surgery.

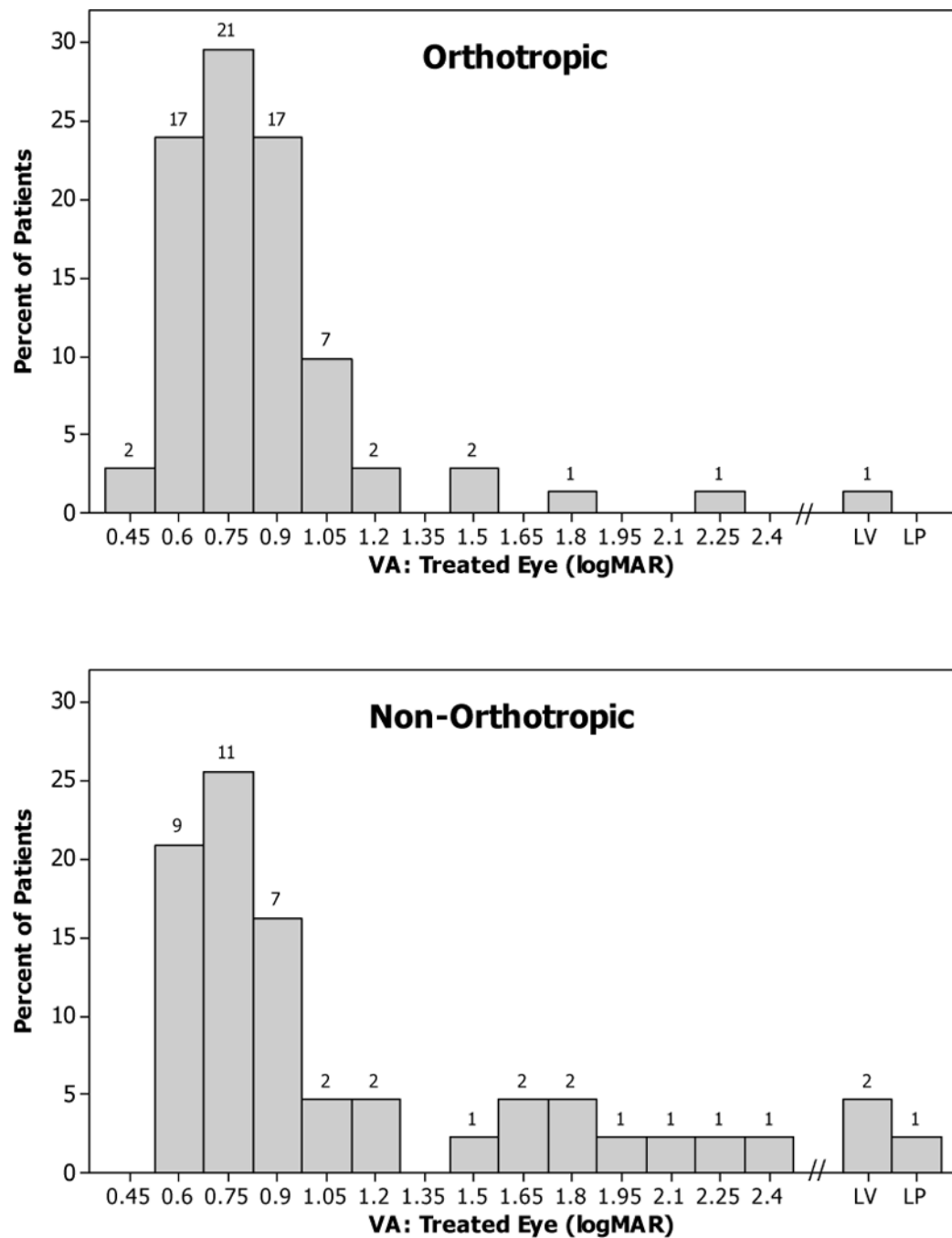


Figure 3.

Histograms showing logarithm of the minimum angle of resolution (logMAR) visual acuity (VA) of treated eyes at 1 year of age. The numbers above the bars indicate the number of patients in the category. Median logMAR VA was 0.80 for orthotropic patients ($n = 71$) and 0.97 for nonorthotropic patients ($n = 43$). LP = light perception; LV = low vision.