VISUAL ACUITY DEVELOPMENT IN INFANTS AND CHILDREN WITH RETINOPATHY OF PREMATURITY: GRATING ACUITY AND LETTER ACUITY RESULTS

Velma Dobson, Ph.D.

Department of Ophthalmology University of Arizona

Abstract

The Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study is a multicenter study involving 23 centers and more than 100 physicians and study center coordinators throughout the United States. The goal of the study is to evaluate the safety and efficacy of retinal ablative cryotherapy for the prevention of retinal detachment and blindness in infants with severe ROP. More than 4,000 infants with birth weights <1251 grams were enrolled in the natural history portion of the study between January 1986 and November 1987. Approximately two-thirds of the infants developed ROP and one-third did not. Two hundred ninety-one infants developed severe ROP and were enrolled in the randomized trial of cryotherapy. All infants in the randomized trial and more than 1,000 of the remaining infants in the natural history part of the study had retinal status evaluated at ages 3 months and 1 year using fundus photographs, and at 3 months, 1, 2, 3, 4, 5 years by physician's examination of the posterior pole of the retina. Visual acuity was evaluated using the Teller acuity card procedure at ages 1, 2, 3, 4, 5 years, using the crowded HOTV letter acuity chart or cards at 3 and 4 years, and using the ETDRS logMAR letter acuity charts at 5 years. Testing was with optical correction, if needed.

This paper describes visual acuity results from children who were participants in the CRYO-ROP study. The first section presents data from the large number of children in the natural history cohort, showing that the development of grating visual acuity depends on the severity of cicatricial ROP (e.g., abnormally straightened temporal retinal blood vessels, macular ectopia, retinal fold or detachment). The second part presents a comparison of grating acuity results with the HOTV letter acuity results collected at ages 3 and 4 years from children in the natural history portion of the study. The final section presents results for grating acuity, HOTV letter acuity, and ETDRS letter acuity testing conducted at ages 1, 3, and 5 years, respectively, in eyes that underwent cryotherapy for severe ROP, as compared with eyes that had severe ROP but did not undergo cryotherapy. Data at all three ages were consistent in showing a clear benefit of cryotherapy in preserving visual function. However, the data also indicated that eyes in which cryotherapy has prevented blindness often do not develop visual acuity that is within the normal range when a child reaches 3 to 5 years of age.
I. Introduction

Retinopathy of prematurity (ROP) is a disease that is characterized by a rapid proliferation of retinal blood vessels in the eyes of infants born prior to term. Infants who develop ROP are at risk for ocular and visual pathway abnormalities, and for deficits in visual function.

The multicenter Study of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) is a 23-center study that was funded in the United States by the National Eye Institute of the National Institutes of Health. The primary purpose of the study was to examine the efficacy and safety of cryotherapy for the treatment of severe ROP. A secondary purpose of the study was to document the natural history of ocular and visual development in eyes that developed ROP and in eyes that did not develop ROP in a large cohort of prematurely-born infants who had birth weights < 1251 grams. The present paper describes the CRYO-ROP study and presents some of the visual acuity results of children who participated in the study.

Two groups of infants were enrolled in the CRYO-ROP study. The first group, called the natural history cohort, were 4,099 infants who had birth weight < 1251 grams, and who were born at one of 23 study centers between January 1986 and November 1987. In order to be eligible for enrollment into the natural history cohort, an infant had to survive for 28 days, a study-certified ophthalmologist had to examine the infant's eyes during interval between 28 and 42 days of life, and the infant's parent(s) had to give consent for the infant to participate in the study. Subsequent to enrollment, infants underwent eye examinations every one to two weeks, in order to document the most severe stage of ROP that developed. Among the 4,099 infants who were enrolled in the natural history cohort, approximately two-thirds developed ROP in one or both eyes, and approximately one-third showed no evidence of ROP on any eye examination (Table 1).

The second group of infants enrolled in the CRYO-ROP study was the randomized cohort. This group consisted of 218 of the infants in the natural history cohort, plus 73 infants from non-study hospitals who were enrolled into the randomized cohort after they developed severe ROP. All infants in the randomized group developed severe ("threshold") ROP, i.e., ROP that was so severe that, if left untreated, it would be expected to produce retinal detachment and blindness in 50% of eyes. The specific ophthalmological definition of threshold ROP is: stage 3 ROP in zone 1 of the retina (the most posterior region of the retina), in the presence of plus disease, or stage 3 ROP in at least 5 contiguous or 8 total sectors (clock hours) of zone 2 of the retina. Plus disease is defined as dilation and tortuosity of the retinal blood vessels in the posterior pole of the retina. These infants who developed threshold ROP participated in the randomized trial of cryotherapy for ROP. In the randomized trial, 240 infants with threshold ROP in both eyes had one eye randomly assigned to cryotherapy and one eye randomly assigned to no cryotherapy. The 51 infants who had threshold ROP in only one eye had that eye randomly assigned to cryotherapy or to no cryotherapy. Mean birth weight of the group of 291 randomized infants was 800 grams, and mean

<table>
<thead>
<tr>
<th>Number of Infants</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>No ROP</td>
<td>1,400</td>
</tr>
<tr>
<td>Any ROP</td>
<td>2,699</td>
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Table 1. Incidence of ROP in Infants in the CRYO-ROP Study

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gestational age at birth was 26.3 weeks.

Follow-up eye examinations of all study participants were conducted when children reached 3 months and 1 year corrected age (post-term age). Further follow-up eye examinations of all natural history participants at five of the study centers (n=1,208) and randomized participants at all 23 study centers (n=291) were conducted at ages 2, 3½, 4½ and 5½ years.

II. Measurement of Grating Visual Acuity in the CRYO-ROP Study

At all follow-up examinations, participants in the CRYO-ROP study had monocular grating visual acuity measured with the Teller acuity card procedure by specially-trained CRYO-ROP Visual Acuity Testers. The Testers did not know which children had developed ROP, nor did they know which, if either, eye of a child had undergone cryotherapy for ROP. Testing was conducted with the child wearing optical correction, if needed.

The procedure used to measure grating visual acuity was the Teller acuity card procedure. This procedure is based on the observation that when infants and children are shown a boldly patterned target paired with a blank target, they will preferentially fixate on the patterned target. The Teller acuity card procedure uses a set of gray cards (Vistech, Dayton, Ohio, USA), each of which has a 12.5 cm by 12.5 cm area of black-and-white grating located to the left or right of a central 4-mm peephole. The spatial frequency (coarseness or fineness) of the grating varies from card to card, over a range from 0.32 to 38 cycles/cm (a cycle is one black and one white stripe). During testing, the infant or child is seated on the parent's lap in front of the Teller acuity card screen, which looks somewhat like a puppet stage (Figure 1). The Tester is seated behind the screen and has the Teller acuity cards stacked face-down, with gratings in order from lower (coarser) to higher (finer) spatial frequency.
Figure 1. Measurement of grating acuity with the Teller acuity card procedure. The infant is seated on the parent's lap, with the eyes at a measured distance from the viewing aperture in the center of the acuity card. The tester (seated behind the screen) presents a series of grating acuity cards and watches the infant's eye and head movements through the viewing aperture. Based on the infant's preferential fixation of the gratings on the cards, the tester estimates acuity as the finest grating that the infant gives evidence of being able to resolve.

frequencies. It is very important that the gratings be face-down, so that the Tester will not know whether the grating on each card is on the left or on the right side. The Tester picks up a card, being careful not to see the front of the card, holds it up to the opening in the screen, and watches the infant or child's eyes. If the grating contains wide stripes, the child will usually look strongly toward one side of the card (left or right). This will lead the Tester to suspect that the stripes are on the side of the card at which the child looked. The Tester will then rotate the card by 180 degrees, so that the stripes are on the opposite side. If the child now looks strongly at the opposite side, the Tester will judge that the grating is on that side and will also judge that the child can resolve the stripes in the grating. The Tester is now permitted to examine the front of the card, to confirm that the child has responded to the location of the grating.

The Tester will now show the child cards containing finer and finer gratings, in sequential order. With each card, the Tester will present the card as many times as necessary to judge whether or not the child can resolve the grating. This may be as few as two times, for a coarse grating to which the child shows strong eye movements, to five or six times, for a finer grating that is near acuity threshold. It is very important that the Tester dose not look at the front of the card until (s) he has decided (yes or no) whether the child can resolve the grating on that card (i.e., whether the child showed consistent looking toward one side of the card). Furthermore, the Tester must use the child's looking behavior to make a decision as to the location of the grating on the card, and must either be certain as to the location of the grating or must decide that the child cannot see the grating, before looking at the front of the card. Keeping the Tester masked to the location of the grating prevents bias and increases the accuracy of the visual acuity measurement. At the end of the test, grating acuity is estimated as the spatial frequency (stripe width) of the finest grating that the child gives evidence of being able to resolve, as judged by the Tester.

III. Grating Acuity Development in Eyes with Retinal Residua of ROP

In the CRYO-ROP study, the Teller acuity card procedure was used to examine the development of grating acuity in eyes with and without retinal residua of ROP. Included in the analysis were eyes from 1,398 CRYO-ROP study participants, and results from examinations conducted at 1, 2, 3½ and 4½ years of age. Data from untreated eyes of children who developed threshold ROP are included in the analysis, but data from eyes...
that underwent cryotherapy are not included.

Retinal residua of ROP are the retinal abnormalities that remain and are observable on fundus examination after the acute-phase of ROP is no longer present.\(^7\) Eyes of preterm infants who never developed acute-phase ROP will show no retinal residua of ROP. Eyes that developed acute-phase ROP may show several types of retinal residua. In the CRYO-ROP study, retinal residua of ROP were categorized in order of severity as follows: (1) eyes with no retinal residua or mild residua located only in the peripheral retina; (2) eyes with macular heterotopia (ectopia), or dragging of the retinal blood vessels; (3) eyes with retinal fold or partial detachment; and (4) eyes with total retinal detachment. In the examinations conducted at ages 3\(\frac{1}{2}\) and 4\(\frac{1}{2}\) years, a subset of eyes in the no/mild residua category was also identified. Eyes in this subset were those with abnormal straightening of the temporal retinal vessels.

As shown in Figure 2, visual acuity results from eyes with quantifiable grating acuity were related to severity of retinal residua of ROP. Eyes that developed ROP but later showed no or only mild peripheral residua showed an average grading acuity that was similar at all ages to that of eyes in which no evidence of acute-phase ROP was ever found. However, the subset of eyes in the no/mild residua category that had abnormal straightening of the temporal retinal vessels at ages 3\(\frac{1}{2}\) and 4\(\frac{1}{2}\) years showed an average grading acuity that was below the range that included the acuity results of 95\% of eyes that never developed ROP. At the 1- and 2-year examinations, eyes with macular heterotopia that had quantifiable visual acuity showed an average grading acuity that was at the lower end of the range that included the acuity results of 95\% of eyes that never developed ROP. By ages 3\(\frac{1}{2}\) and 4\(\frac{1}{2}\) years, however, these eyes with macular heterotopia showed an average grading acuity that was far below this normal range. Many of the eyes with retinal fold or partial retinal detachment did not have quantifiable grading acuity. As shown in Figure 2, those that did have a quantifiable grading acuity showed an average acuity that, at all ages, was well below the range of acuity values obtained from eyes that never developed ROP.

In summary, retinal residua of ROP occur along a continuum of severity from no observable residua to retinal detachment. Functionally, this continuum is reflected in an increasing severity of grading visual acuity deficits. Eyes with no residua or only mild residua show acuity results that are very similar to those of preterm infants whose eyes did not develop ROP. Eyes with abnormally straightened temporal retinal blood vessels
show reduced acuity, at least at 3½ and 4½ years of age. Eyes with macular heterotopia show an average acuity deficit that is greater than that of eyes with abnormally straightened temporal vessels. Finally, eyes with retinal fold or partial retinal detachment show extremely poor grating visual acuity, if their acuity is good enough to be measurable.

IV. Comparison of Recognition (Letter) and Grating Visual Acuity Results

In infants, it is not possible to measure recognition (letter) visual acuity. However, by about age 3 years, many children can match letters, so that they can be tested with a simplified letter acuity test. One letter acuity test that has been developed for use with young children is the Crowded HOTV chart and cards (Good-Lite, Chicago, Illinois, USA). The test uses only 4 letters (H, O, T, and V), all of which are left-right symmetrical. Use of symmetrical letters avoids the left-right reversal problem demonstrated by some young children. The crowded HOTV test has the further advantage that each letter has "crowding bars" to the left and right sides. These bars simulate the presence of adjacent letters on a line-acuity chart, which allows the Tester to present only one letter at a time without overestimating visual acuity, as often occurs when amblyopic children are tested with isolated single letters.

In the CRYO-ROP study, the examinations conducted at ages 3½ and 4½ years included measurement of grating acuity with the Teller acuity card procedure, and recognition (letter) visual acuity with the crowded HOTV test. Results from the two visual acuity tests were compared in two groups of eyes: (1) "normal" eyes, in which the eye examination showed no evidence of retinal residua of ROP, amblyopia, nystagmus, or optic atrophy, and no evidence in the child of developmental delay, strabismus, or anisometropia; and (2) eyes with retinal residua of ROP, including abnormally straightened temporal retinal blood vessels, macular heterotopia, retinal fold, or partial retinal detachment. None of the eyes included in the analysis had undergone cryotherapy. Figure 3 shows the difference (in octaves) between the HOTV score and the grating acuity score in

![Graph showing the difference between HOTV and grating scores]

Figure 3. Difference, in octaves, between HOTV and grating acuity in normal eyes (stippled area), and in eyes with abnormally straightened temporal retinal blood vessels (dashed line) and eyes with macular heterotopia (solid line), tested at age 4½ years. (Reprinted with permission.)
1,337 normal eyes, 19 eyes with straightened acuity temporal retinal blood vessels, and 55 eyes with macular heterotopia, tested at age 4½ years. Acuity scores for the two types of tests were equated based on the convention that 6/6 (20/20) letter acuity is equivalent to grating acuity of 30 cycles/degree. As shown in Figure 3, the difference between letter acuity and grating acuity in normal eyes rarely exceeded 0.75 octave, and on average, HOTV acuity was 0.27 octave better than grating in these eyes. The average difference of 0.27 octave is approximately equivalent to one line on a logMAR acuity chart (An octave is a halving or doubling of acuity, e.g. from 6/6 (20/20) to 6/12 (20/40) letter acuity, or from 30 to 15 cycles/degree grating acuity.)

In eyes with retinal residua of ROP, the difference between HOTV and grating acuity was more variable, and was related to the eye's level of letter acuity. Eyes with HOTV acuity of about 20/150 or better tended to show better letter acuity than grating acuity, similar to the results found in normal eyes. In contrast, eyes with acuity worse than about 20/150 tended to show better grating acuity than letter acuity. These results are similar to those reported previously in eyes with visual acuity deficits due to macular degeneration or amblyopia.8

V. Acuity Results from Treated vs. Control Eyes in the Cryotherapy Trial

The results of the CRYO-ROP study that are presented in Figures 2 and 3 are based on data from eyes of children in the natural history portion of the study, and do not include results from eyes that underwent cryotherapy. The purpose of this final section of the paper is to compare visual acuity results from eyes that developed threshold ROP and were randomly assigned not to undergo cryotherapy. The acuity comparisons presented in this section of the paper are based on data from the 291 children who were participants in the randomized trial of cryotherapy. Results are presented from three follow-up ages:(1) Teller acuity card grating acuity results measured at age 1 year;9 (2) crowded HOTV recognition (letter) acuity results measured at age 3½ years;10 and (3) recognition (letter) acuity results obtained with the Early Treatment for Diabetic Retinopathy Study (ETDRS) logMAR acuity charts11 at age 5½ years.12

For data analysis, acuity scores were classified as "favorable" or "unfavorable". Favorable grating acuity scores were those that were within the normal range or no more than 1 octave below the normal range, based on the child's age. Unfavorable grating acuity scores were those that were more than 1 octave below the normal range, based on age. At age 1 year, unfavorable grating acuity scores were those that were worse than 0.8 cycles/degree. Favorable recognition acuity scores at both 3½ and 5½ years were those that were better than 6/60 (20/200); unfavorable scores were those that were 6/60 (20/200) or worse.

Figure 4 compares the proportion of eyes in the cryotherapy (treated) group and in the no-cryotherapy (control) group that had unfavorable visual acuity outcomes at 1, 3½ and 5½ years. At all three ages, cryotherapy had a clearly beneficial effect on visual acuity outcome. Unfavorable visual acuity outcomes were found in 35.0% of treated eyes and 56.3% of control eyes at 1 year, in 46.6% of treated eyes and 57.5% of control eyes at 3½ years, and in 47.1% of treated eyes and 61.7% of control eyes at 5½ years. Thus, there were 38% fewer unfavorable outcomes in treated eyes than control eyes at 1 year(p<0.01), 19% fewer at
Figure 4. Proportion of cryotherapy-treated and control eyes with unfavorable visual acuity outcomes at ages 1, 3½ and 5½ years. Number of treated eyes: 191 at 1 year, 207 at 3½ years, 208 at 5½ years. Number of control eyes: 194 at 1 year, 205 at 3½ years, 207 at 5½ years.

3½ years (p<0.01), and 24% fewer at 5½ years (p<0.01). These results indicate that at all three follow-up ages, cryotherapy had a beneficial effect on visual acuity outcome in eyes with severe ROP.

A more detailed examination of the visual acuity results of cryotherapy-treated and control eyes is shown in Figures 5, 6 and 7. In these figures, acuity is categorized as normal for age, below normal for age, poor, or blind. Eyes in the "normal" category at 1 year had grating acuity of 1.6 cycles/degree or better. At 3½ years, eyes in the "normal" category had acuity of 6/15 (20/50) or better, and at 5½ years, eyes in the "normal" category had acuity of 6/12 (20/40) or better. Eyes in the "below normal" category at one year had grating acuity better than or equal to 0.8 cycles/degree and worse than 1.6 cycles/degree. At 3½ years, the "below normal" category included those eyes with letter acuity better than 6/60 (20/200) and worse than 6/15 (20/50), and at 5½ years the "below normal" category included eyes with acuity better than 6/60 (20/200) and worse than 6/12 (20/40). The "poor" category included eyes with measurable grating acuity worse than 0.8 cycles/degree at 1 year; and eyes...
with measurable letter acuity of 6/60 (20/200) or worse at 3½ or 5½ years. Eyes classified as "blind" included those with no light perception, light perception only, or gross pattern vision as evidenced by a response to the 2.2-cm-wide stripes on the Teller Low Vision acuity card.

The results shown in Figure 5 indicate that, at age 1 year, the distribution of acuity results was bimodal: eyes were either blind or showed acuity in the normal range for a 1-year-old. There were more treated eyes than control eyes with acuity in the normal range, and fewer treated eyes than control eyes that were blind. Thus, eyes that were saved from blindness by cryotherapy showed acuity in the normal range at age 1 year.

As shown in Figure 6, the results were different at age 3½ years. The distribution of acuity scores was no longer bimodal. Instead, acuity scores were distributed across all four acuity categories. While there were still many fewer treated eyes than control eyes in the blind category, there were equal numbers of treated eyes and control eyes with acuity scores in the normal range. The higher proportion of treated eyes than control eyes in the below normal and poor categories suggests that eyes that were saved from blindness by cryotherapy did not show normal acuity development between ages 1 year and 3½ years. Instead, acuity development lagged behind that of normal eyes, so that these eyes that were saved from blindness by cryotherapy now showed acuity scores in the below normal or poor category.

The results at age 5½ years (Figure 7) were similar to those at 3½ years, except that there were more control eyes than treated eyes with acuity in the normal range. These results support the conclusion that acuity development is not normal in eyes in which cryotherapy has prevented retinal detachment and blindness.

In summary, cryotherapy has a clearly beneficial effect in preventing retinal detachment and blindness in eyes with severe acute-phase ROP, and this beneficial effect of cryotherapy is maintained for at least 5½ years. Most eyes in which cryotherapy has prevented blindness show acuity that is in the normal range at age 1 year, when visual acuity, even in normal infants, is substantially below adult values. Between ages 1 and 3½ years, eyes in which cryotherapy has prevented blindness fail to show the improvement in visual acuity that occurs in normal, healthy eyes. As a result, most of these eyes show acuity scores in the below normal or poor range at age 3½ years. At 5½ years, eyes in which cryotherapy has prevented blindness continue to show acuity scores in the below normal or poor range, and there is a suggestion (not statistically significant) that eyes that underwent cryotherapy are less likely than control eyes to attain normal visual acuity. Thus, cryotherapy is clearly beneficial in preventing blindness in at least some eyes with severe ROP. However, these eyes do not develop completely normal visual function.

VI. Future Directions

The CRYO-ROP study was the first large-scale study of the efficacy and safety of cryotherapy for severe ROP. Long-term follow-up of children in the randomized group of study participants is continuing. Recently, collection of data on ocular structure and visual function at age 10 years was completed, and further follow-up until age 15 years is being considered. Ancillary studies that arose from the CRYO-ROP study include the Supplemental Therapeutic Oxygen for Prethreshold ROP (STOP-ROP) study that is currently examining the effects of supplemental oxygen on reducing the incidence of ROP, and the Trial of Light Reduction for Reducing Frequency of
ROP (LIGHT-ROP) study that recently reported a failure to find an effect of Neonatal Intensive Care Unit light level on the incidence of ROP. More recently, a study to examine the effect of retinal ablative therapy (laser or cryotherapy) on moderate ROP has been proposed and submitted for funding. This study would compare the structural and functional outcomes of eyes with moderate ROP randomized to cryotherapy prior to reaching conventional threshold for treatment with structural and functional outcomes of eyes with moderate ROP that were randomized to postponement of treatment with cryotherapy until conventional threshold severity for treatment was reached. It is likely that all of these studies will increase our understanding of ROP and will aid in finding ways to prevent the devastating blindness that continues to occur in the very low birth weight population.

Acknowledgments: The author thanks the physicians, study personnel, parents, and children who participated in the CRYO-ROP study. The CRYO-ROP study and preparation of this paper were supported by National Institutes of Health/National Eye Institute grants U10EY05874 and U10EY08176, respectively.

References


