Effect of Retinal Ablative Therapy for Threshold Retinopathy of Prematurity

Results of Goldmann Perimetry at the Age of 10 Years

Cryotherapy for Retinopathy of Prematurity Cooperative Group

Objective: To examine monocular visual fields at the age of 10 years in children with birth weights less than 1251 g in whom severe acute-phase retinopathy of prematurity (ROP) developed in 1 or both eyes and who had random assignment of eyes to cryotherapy (treated) or no cryotherapy (control) and in a comparison group of children who did not develop ROP in the neonatal period.

Methods: Subjects were 255 children who developed severe ROP and 104 children who did not develop ROP. All were born between January 1, 1986, and November 30, 1987, and had birth weights of less than 1251 g. Goldmann perimetry was used to measure visual field extent along 8 meridia (15°, 60°, 105°, 150°, 195°, 240°, 285°, and 330°) using the V4e and III4e stimuli. Data were analyzed by quadrant and overall solid angle of the area of the retina sensitive to the test stimulus.

Results: When blind eyes were assigned a score of 0, visual field area was 24% to 26% larger in treated eyes than in control eyes. When data from only patients with 1 sighted treated eye and 1 sighted control eye were examined, visual field area was 5% smaller in treated eyes than in control eyes. For these patients, visual field area was reduced by 30% to 37% in treated eyes and by 27% to 33% in control eyes compared with eyes with no ROP.

Conclusions: Cryotherapy preserves peripheral vision in eyes with severe ROP by preserving sight in these eyes. After excluding 70 blind treated and 102 blind control eyes, data from eyes with quantifiable visual fields indicate that cryotherapy produces a small reduction of visual field area in eyes with severe ROP. With or without cryotherapy, visual field area is considerably smaller in eyes that had severe acute-phase ROP than in eyes of preterm children who did not develop ROP.


TREATMENT for severe acute-phase (threshold) retinopathy of prematurity (ROP) involves ablation of the peripheral retina and, as such, would be expected to reduce peripheral visual field. Five previous reports have assessed visual field extent after laser photocoagulation or cryotherapy for severe ROP. Two of these studies used the white-sphere kinetic perimetry method described by Mohn and van Hof-van Duin. This is a relatively simple technique that uses a large peripheral target and is especially useful in infants and young children. In 1992, Fetter et al reported normal binocular visual field extent in 8 of 10 one-year-old children who had undergone cryotherapy in both eyes for severe ROP. More recently, the multicenter study of cryotherapy for ROP (CRYO-ROP) compared data from eyes that had undergone cryotherapy for severe acute-phase ROP with data from eyes with equivalent severity ROP that had not undergone cryotherapy in 78 children aged 5½ years. When only pairs of sighted eyes were considered, visual fields of treated eyes were approximately 6° smaller than those of control eyes.

See also pages 1110, 1129, and 1200

Using the more standard technique of Goldmann kinetic perimetry, Tamai et al showed visual field restriction in eyes of 6 of 11 children, and Takayama et al showed deficits in the eyes of 13 of 13 children who had received laser photocoagulation or cryotherapy for severe ROP. However, both studies compared the results of treated eyes with results of eyes that did not develop severe ROP. Therefore, it is not possible from these studies to determine whether the visual field abnormalities resulted from severe ROP itself or from treatment of the disease. In another small
SUBJECTS AND METHODS

PATIENTS

Eligible subjects were the 255 survivors of the 291 infants who participated in the randomized trial of CRYO-ROP. All subjects were born between January 1, 1986, and November 30, 1987, and had birth weights of less than 1251 g. The 291 infants who participated in the randomized trial had developed threshold ROP in 1 or both eyes during the neonatal period (threshold ROP was defined as 3 contiguous or 8 cumulative clock hours of stage 3+ ROP in zone 1 or zone 2). Threshold ROP was found in both eyes at the same examination in 240 infants (bilateral threshold ROP), and one eye was randomly assigned to undergo cryotherapy and the other assigned to serve as a control. The remaining 51 infants developed threshold ROP in only 1 eye, and that eye was randomly assigned to receive cryotherapy or to serve as a control.15 At 1 participating center (Philadelphia, Pa), a comparison group of 104 CRYO-ROP study participants who did not develop ROP during the neonatal period9 were eligible to participate in the 10-year study examination.

Informed consent was obtained from parents before each child's entry into the study, before randomization if the child developed threshold ROP, and at entry into both the 5½-year and 10-year follow-up phases of the study. Extensive descriptions of the study population have been published elsewhere.8,10-12

PROCEDURES

Goldmann Visual Field Testing

Monocular visual field extent was measured along the 15°, 60°, 105°, 135°, 150°, 195°, 240°, 285°, and 330° meridia using a Goldmann perimeter that has a radius of 300 mm and a background luminance of 31.5 apostilb. These meridia were selected because of mechanical limitations of testing the horizontal and vertical meridia using the Goldmann apparatus. Each subject's right eye was tested first, using the V4e stimulus followed by the III4e stimulus. Then the left eye was tested with both the V4e and III4e stimuli. Each stimulus was moved at approximately 3° per second, and for each stimulus a nonsystematic order of testing at the 8 meridia was used. Testing was performed after instillation of cycloplegic drops and without spectacle correction.

Perimetry was conducted by a tester who was masked to the eye's treatment status. During testing, the child was instructed to fixate on the black dot at the center of the perimeter and to press the buzzer as soon as the stimulus was visible in the periphery. The tester made 1 presentation on each meridian for each target size. However, a second presentation was permitted if the tester was not confident of the validity of the response (eg, the child showed poor fixation). The second presentation could be performed at any time during the test with that stimulus size.

Eye Examinations

Eye examinations, which included cycloplegic retinoscopy and assessment of ROP residua, were performed by study-certified ophthalmologists. Cycloplegia was achieved using 1% cyclopentolate hydrochloride. When cyclopentolate was medically contraindicated, 1% tropicamide was used.

DATA ANALYSIS

Both treated and control eyes of children who participated in the randomized trial are included in the analysis. For children in the no ROP group, 1 eye was randomly selected for inclusion in the analysis.

Using a previously described visual field analysis program,9 the shape and extent of the peripheral visual field were computed for each eye by mathematically projecting the distances and directions of the isopters for the 8 meridia tested onto the surface of a hemisphere and calculating the solid angles in square degrees of the polygon this creates. This solid angle reflects the area of retina sensitive to the test target used for each isopter and avoids the cartographic distortion inherent in measurements taken directly from the Goldmann perimetry charts, which represent azimuthal equidistant polar projections.

Because of the expected possible regionality of the disturbance of retinal function by ROP and the possible regionality of any effect of cryotherapy, regional function was assessed by quadrants. Isopters were constructed at 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315° by non-Euclidean extrapolation of the closest adjacent data points. The solid angle of the 4 quadrants created by the 45°, 135°, 225°, and 315° isopters then was used to determine the relative retinal function of the superonasal, superotemporal, inferotemporal, and inferonasal quadrants. To provide a graphic representation and comparison of the visual field data from treated and control eyes, data from left eyes were transposed and presented as if for right eyes.

Statistical analyses were done comparing treated eyes and control eyes. The Wilcoxon signed rank test was used to test whether the groups had different visual field areas.

case series, Quinn et al2 compared 8 treated with 6 control eyes of 8 patients and found that eyes that had retinal structure and acuity preserved following cryotherapy for severe ROP had somewhat smaller visual fields than the control eyes in which vision was preserved. This result suggested that cryotherapy may produce a small reduction in visual field extent in eyes with severe ROP.

The purpose of this article is to report Goldmann kinetic perimetry results from the 10-year study examination of the CRYO-ROP study. Visual field results from eyes with severe ROP that underwent cryotherapy are compared with results from eyes with equivalent severity of ROP that did not undergo cryotherapy. This analysis permits an assessment of whether the benefit in using cryotherapy to preserve retinal structure is achieved at the cost of a serious deficit in peripheral visual field extent. For further comparison, visual field results are presented from a group of children in the CRYO-ROP study who were not observed to develop ROP during the neonatal period (no ROP). This allows an evaluation of the effect of serious ROP (with or without cryotherapy) on visual field extent in children who had birth weights
Visual Field Area for Eyes That Had No Retinopathy of Prematurity (ROP) During the Neonatal Period and for Eyes That Were Randomized to Receive Cryotherapy or No Cryotherapy

<table>
<thead>
<tr>
<th>Direction</th>
<th>No ROP (n = 85)</th>
<th>Treated (n = 205/202)†</th>
<th>Control (n = 203/202)‡</th>
<th>Randomized Eyes With Quantifiable Field</th>
<th>Bilateral Threshold ROP With Quantifiable Field in Both Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treated</td>
<td>Control‡‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 135/132)§</td>
<td>(n = 101/100)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 80/78)‡</td>
<td>(n = 80/78)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V4e stimulus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>1953 (509)</td>
<td>809 (805)</td>
<td>643 (824)</td>
<td>1228 (684)</td>
<td>1306 (704)</td>
</tr>
<tr>
<td>Superior</td>
<td>2415 (649)</td>
<td>1921 (1766)</td>
<td>1523 (1834)</td>
<td>2918 (1348)</td>
<td>3138 (1332)</td>
</tr>
<tr>
<td>Inferior</td>
<td>2794 (509)</td>
<td>1266 (1172)</td>
<td>1011 (1219)</td>
<td>1923 (906)</td>
<td>2076 (697)</td>
</tr>
<tr>
<td>Total</td>
<td>10 970 (1856)</td>
<td>4958 (4404)</td>
<td>3893 (4617)</td>
<td>7436 (3242)</td>
<td>7987 (3228)</td>
</tr>
</tbody>
</table>

Inferior 4e stimulus

|                 |                |                        |                        |                                        |                                                           |
|                 |                | (n = 135/132)§         | (n = 101/100)§         |                                        |                                                           |
|                 |                | (n = 80/78)‡           | (n = 80/78)‡           |                                        |                                                           |
| Nasal           | 1776 (452)     | 622 (686)              | 520 (684)              | 952 (637)                              | 1054 (617)                                              |
| Temporal        | 3919 (705)     | 1638 (1591)            | 1278 (1628)            | 2506 (1282)                            | 2620 (1362)                                             |
| Superior        | 1808 (562)     | 692 (706)              | 558 (718)              | 1059 (612)                             | 1140 (613)                                              |
| Inferior        | 2556 (510)     | 1048 (1026)            | 863 (1095)             | 1603 (847)                             | 1771 (910)                                              |
| Total           | 10 059 (1850)  | 4008 (3834)            | 3219 (4008)            | 6120 (3078)                            | 6585 (3211)                                             |

*Data are given as mean (SD) visual field area in square degrees.
†Blind eyes are assigned a visual field extent on 0° in all meridia.
‡First n for V4e isopter; second n for II4e isopter.

Of the 255 eligible subjects who had threshold ROP, 247 children (96.9%) completed the 10-year study examination. There were 202 children who had bilateral threshold ROP, yielding data on 202 treated and 202 control eyes. Forty-five children had unilateral threshold disease, yielding 25 treated and 20 control eyes. Visual field data were obtained from 205 of the 227 treated eyes and from 203 of the 222 control eyes. Visual field data were not obtained from 22 treated and 19 control eyes primarily due to developmental delay. Of the 104 eligible subjects in the no ROP group, 102 (98.1%) participated in the 10-year examination and visual field data were obtained from 85 of these children. Goldmann perimeter could not be arranged for the remaining 17 children.

The Table presents, for the V4e and II4e isopters, the mean temporal, inferior, nasal, and superior visual field areas in square degrees for eyes in the no ROP group (left data column), for all eyes in the treated and control groups (next 2 data columns), for treated eyes and control eyes with quantifiable visual fields (next 2 data columns), and for treated eyes and control eyes of patients with bilateral threshold ROP who had measurable field in both eyes. When data from all eyes in the treated, control, and no ROP groups are compared (first 3 data columns), treated eyes have visual fields that are larger by about 24% to 26% than control eyes, and both have smaller visual fields than eyes in the no ROP group. These results are shown graphically in Figure 1A for the V4e isopter and Figure 1B for the II4e isopter.

In the Table, data from treated and control eyes with quantifiable visual fields are presented in the fourth and fifth data columns. These data, in which results from 70 blind treated and 102 blind control eyes have been excluded, suggest that treated eyes have smaller visual field extent than control eyes by about 7%. Interpretation of these data is confounded by the inclusion of 2 eyes from some patients and 1 eye from other patients. Therefore, we examined data from the subset of patients who had bilateral threshold ROP (1 treated eye and 1 control eye) and in whom both eyes provided measurable visual fields (right 2 data columns). These data indicate that treated eyes have smaller visual field extent than control eyes by about 5%. Matched-pairs signed rank tests conducted on data from this subset of patients indicated that visual field extent was significantly smaller for treated than for control eyes only in the inferior visual field (P < .05 for both isopters). Comparison of data from eyes in this same subset of patients to data from eyes in the no ROP group (left data column) showed that visual field extent was smaller in eyes with severe ROP but had sufficient acuity to permit quantification of visual field extent than in eyes that did not develop ROP. Data from treated and control eyes in patients with bilateral threshold ROP who had measurable field extent are shown graphically in Figure 2A for the V4e isopter and in Figure 2B for the II4e isopter. For comparison, data from the no ROP group that were shown in Figure 1 are replotted in Figure 2.

The present study used standard Goldmann kinetic perimetry to assess visual fields of the children in the CRYO-ROP study who had severe ROP and who were examined at the age of 10 years, as well as a comparison group of CRYO-ROP study participants who did not develop ROP during the neonatal period. The results indicated a benefit of cryotherapy in preserving peripheral vision in eyes with severe ROP, with control eyes showing 24% to 26% smaller visual field area than treated eyes (Figure 1, comparison of treated and control eyes). Thus, cryo-
Figure 1. Visual field extent for all treated eyes, all control eyes, and all eyes that did not develop retinopathy of prematurity (ROP) tested using Goldmann kinetic perimetry with (A) V4e stimulus and (B) III4e stimulus. For the purpose of presentation, data from left eyes were transposed and presented as if for right eyes. Blind eyes are assigned a visual field extent of 0° in all meridia. For the V4e stimulus, data from 205 treated eyes (dashed line), 203 control eyes (solid line), and 85 no ROP eyes (labeled solid line) are presented. For the III4e stimulus, data from 202 treated eyes, 202 control eyes, and 85 no ROP eyes are presented.

Figure 2. Quantifiable visual field results (blind eyes excluded) of treated eyes, control eyes, and eyes that did not develop retinopathy of prematurity (ROP). Eyes were tested with Goldmann kinetic perimetry using (A) V4e stimulus and (B) III4e stimulus. For the purpose of presentation, data from left eyes were transposed and presented as if for right eyes. For the V4e stimulus, data from 135 treated eyes (dashed line), 101 control eyes (solid line), and 85 no ROP eyes (labeled solid line) are presented. For the III4e stimulus, data from 132 treated eyes, 100 control eyes, and 85 no ROP eyes are presented.

therapy preserves peripheral vision in eyes with severe ROP by permitting eyes that would otherwise be blind to retain a measurable visual field.

Comparison of visual fields in treated and control eyes in which vision was preserved (Figure 2) showed a 7% reduction in the area of the visual field in the treated eyes. This potential adverse effect of cryotherapy is small and likely of little functional importance. Thus, the results presented in Figure 1 support the benefit of cryotherapy, and the results presented in Figure 2 demonstrate a relatively small decrease in visual field area in treated eyes in which vision was preserved.

In the present study, a large difference is noted between visual field extent in eyes of low-birth-weight infants who did not develop ROP (CRYO-ROP patients from the Philadelphia participating center) and eyes of low-birth-weight infants who developed threshold ROP (CRYO-ROP patients from all 23 participating centers). As shown in Figures 1 and 2, visual field extent was substantially smaller in eyes that developed threshold ROP than in eyes that did not develop ROP, irrespective of whether eyes with threshold ROP underwent cryotherapy. Comparison of visual field area in eyes that did not develop ROP with visual field area in sighted eyes with severe ROP that did not undergo cryotherapy (control eyes, third column from right in the Table) showed a reduction in the area of the visual field in control eyes of 27.2% for the V4e stimulus and 34.5% for the III4e
stimulus. The reduction in visual field area was slightly larger in treated eyes with quantifiable visual fields (32.2% for the V4e stimulus and 39.1% for the III4e stimulus). Thus, among sighted eyes, severe ROP has a much more detrimental effect on peripheral vision than does peripheral retinal ablation used to treat severe ROP. However, this conclusion is only tentative because of differences in demographic characteristics between CRYO-ROP study participants who did not develop ROP and study participants who developed severe ROP. That is, although all CRYO-ROP study participants had birth weights less than 1251 g, those who did not develop ROP were generally of higher birth weight and had fewer medical complications than did those who developed severe ROP.

Previously, we reported visual field results from a subset of 78 children from 5 of the 23 CRYO-ROP study centers.3 These children had developed severe acute-phase ROP during the neonatal period and were tested with white sphere kinetic perimetry at the age of 5½ years. Results indicated a clear benefit of cryotherapy in preserving peripheral vision in eyes with severe ROP, but suggested that an adverse effect of preservation of vision was a small (10%) reduction in visual field extent compared with sighted eyes with severe ROP that did not receive cryotherapy. The results of the present study, conducted nearly 5 years later using a standard adult perimetry procedure, confirmed the earlier report of a clear benefit of cryotherapy in preserving peripheral vision in eyes with severe ROP. Similar to the results at 5½ years, there was a 5% to 7% reduction in the area of the visual field among sighted eyes treated with cryotherapy compared with sighted control eyes that had similar severity of ROP. Thus, even though different methods were used to measure visual fields, both the 5½- and 10-year results produced essentially similar findings.

In contrast, the reduction in visual field area observed at the 10-year examination in sighted eyes with severe ROP, compared with eyes that did not develop ROP, was not observed in the visual field results from the 5½-year examination. At 5½ years, sighted eyes with severe ROP showed visual field extent that was nearly identical to that measured in the group of eyes that did not develop ROP. This difference in visual field results at 5½ and 10 years may be related to differences in methods. At the 5½-year examination, the stimulus was a relatively large (6°) white sphere mounted on a black wire and moved centrally in front of a black background. In contrast, the 2 stimuli used at the 10-year examination were small lights (V4e [approximately 2°] and II4e [approximately 0.5°]) that were moved centrally in front of a white background. It is likely that using smaller, low-contrast stimuli at the 10-year examination may have demonstrated more subtle deficits in visual field extent in sighted eyes with severe ROP.

Three previous studies have used Goldmann perimetry to examine peripheral vision in children with severe ROP whose eyes underwent peripheral retinal ablation. Tamai et al5 and Takayama et al6 both reported that visual field extent was smaller in eyes with severe ROP that underwent peripheral retinal ablation than in normal eyes. The results of the present study suggest that most of this deficit was related to the presence of severe ROP rather than to the surgical intervention (cryotherapy or laser ablation) for the disease. Quinn et al7 studied a small number of children with severe ROP and reported a visual field deficit of approximately 20% in sighted eyes that received cryotherapy compared with control eyes. Results of the present study confirmed that there is a deficit in sighted, cryotherapy-treated eyes, but it is not of the magnitude previously found by Quinn et al.2

In summary, the results of the present study show a reduction of approximately 5% to 7% in visual field area in the treated eyes of 10-year-old patients with bilateral threshold ROP in whom both the treated and control eyes showed quantifiable visual fields. This reduction is similar to the reduction of approximately 10% in visual field extent observed in our visual field assessment of the same study population at the age of 5½ years. The consistency of this finding, despite differences in age, methods, and data analysis techniques, reinforces our earlier conclusion that cryotherapy of the peripheral avascular retina in eyes with severe ROP may produce a small but measurable reduction in visual field extent. The benefit of peripheral retinal ablation in preventing retinal detachment in eyes with severe ROP clearly outweighs the risk of this potential reduction in visual field extent. This is particularly apparent when the blind eyes are assigned a score of 0 visual field area (Figure 1). However, caution is needed in applying peripheral retinal ablation in eyes with less severe ROP, which have a lower risk for blindness, because these eyes may develop visual field deficits as a result of the surgical intervention.

An important finding in the present study is the marked (27% to 35%) deficit in the area of the visual field noted in sighted eyes that had severe ROP during the neonatal period but were not treated with cryotherapy. This finding was not apparent until children could be tested with standard adult perimetry. Thus, in addition to the ROP-related morbidity that can be observed early in life, eg, retinal scarring, myopia, strabismus, and blindness,5,12 severe ROP produces more subtle change that only becomes measurable later in life. This finding underscores the necessity of observing the child with severe ROP throughout life and supports the importance of continued efforts to prevent severe ROP through improved medical and/or surgical management of the very low-birth-weight infant.

Accepted for publication June 16, 2000.

The CRYO-ROP study is supported by cooperative agreement U10 EY05874 from the National Eye Institute, National Institutes of Health, US Department of Health and Human Services, Bethesda, Md.

We thank the writing committee for this article: Graham E. Quinn, MD (chair); Velma Dobson, PhD, Richard Weleber, MD, Robert J. Hardy, PhD, Earl A. Palmer, MD, Dale L. Phelps, MD, C. Gail Summers, MD, and Betty Tung, MS.

Corresponding author: Graham E. Quinn, MD, Division of Pediatric Ophthalmology, The Children's Hospital of Philadelphia, First Floor, Wood Bldg, Philadelphia, PA 19104.
REFERENCES


Archives Web Quiz Winner

Congratulations to the winner of our April quiz, David S. Walton, MD, Boston, Mass. The correct answer to our April challenge was posttransplant lymphoproliferative disorder. For a complete discussion of this case, see the Clinopathologic Reports, Case Reports, and Small Case Series section in the May ARCHIVES (Cook T, Grostern RJ, Barney NP, Mills MD, Judd R, Albert DM. Posttransplant lymphoproliferative disorder presenting as iris mass and uveitis. Arch Ophthalmol. 2001;119:768-770).

Be sure to visit the Archives of Ophthalmology World Wide Web site (http://www.archophthalmol.com) and try your hand at our Clinical Challenge Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of the book One Hundred Years of JAMA Landmark Articles.