Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: Preliminary Results

Cryotherapy for Retinopathy of Prematurity Cooperative Group

From the Cryotherapy for Retinopathy of Prematurity Cooperative Group and the National Eye Institute, Bethesda, Maryland

ABSTRACT. We report the preliminary 3-month outcome of a multicenter randomized trial of cryotherapy for treatment of retinopathy of prematurity (ROP). Transscleral cryotherapy to the avascular retina was applied to one randomly selected eye when there was threshold disease (defined as five or more contiguous or eight cumulative 30° sectors [clock hours] of stage 3 ROP in zone 1 or 2 in the presence of "plus" disease). An unfavorable outcome was defined as posterior retinal detachment, retinal fold involving the macula, or retrolental tissue. At this writing, 172 infants had been examined 3 months after randomization. An unfavorable outcome was significantly less frequent in the eyes undergoing cryotherapy (21.8%) compared with the untreated eyes (43%). While the surgery was stressful, no unexpected complications occurred during or following treatment. These data support the efficacy of cryotherapy in reducing by approximately one half the risk of unfavorable retinal outcome from threshold ROP. Pediatrics 1988;81:697-706; cryotherapy, retinopathy of prematurity.

Transscleral cryotherapy to the avascular peripheral retina of premature infants with retinopathy of prematurity (ROP) has been used clinically since 1972 in Japan4–5 and has gained acceptance in other parts of the world.6,7 In the United States, however, there has been some reluctance to embrace this form of therapy, in part because of reports of adverse consequences8–10 and in part because of a lack of controlled trials. Nevertheless, clinical experience indicating its safety and various levels of efficacy has continued to accumulate.11–15

To resolve the uncertainty about the value of this treatment, a multicenter trial of cryotherapy for ROP (the CRYO-ROP Study) was designed to evaluate its safety and efficacy. Premature infants of very low birth weight are often in fragile health, and the degree of benefit of cryotherapy (both short- and long-term) should be known to weigh the benefit against the medical risk of treatment.

Herein we report the preliminary results of the CRYO-ROP Study, based on 172 infants. These infants have completed the 3-month evaluation following cryotherapy and, at this writing, 45 of them had been followed up for 1 year after randomization.

PATIENTS AND METHODS

Eligible patients included those born on Jan. 1, 1986, or later weighing less than 1,251 g. Informed consent was obtained for initial ophthalmic examinations to begin at 4 to 6 weeks of age. Because of the unpredictability of ROP and the possibility of very rapid progression, examinations were repeated every 2 weeks unless the ROP reached a "prethreshold" (zone 1, any stage; zone 2, stage 2 [ridge] with "plus" disease [defined here as a certain degree of dilatation and tortuosity of the retinal blood vessels in the posterior pole of the eye], or zone 2, stage 3 [ridge with extraretinal fibrovascular proliferation]).16 Examinations were then repeated at least weekly until the progression to threshold disease, a level of severity at which the risk of blindness was predicted to approach 50%. Threshold disease was defined as at least five contiguous or eight cumulative 30° sectors (clock hours) of stage 3 ROP in zone 1 or 2, in the presence of plus disease (Figs 1 and 2). When this disease state was confirmed indepen-
contiguous clock-hour sectors

Fig 1. Diagram of two representative eyes that have reached threshold for randomization. Right eye (RE): at least eight cumulative 30° sectors (clock hours) of stage 3. Left eye (LE): at least five contiguous 30° sectors of stage 3. Thin line of retinopathy of prematurity represents stage 1 or 2, and broader sketched line signifies stage 3.

Fig 2. Standard photograph of "plus" disease. Degree of vascular dilatation and tortuosity shown here represents minimum acceptable abnormality to categorize a fundus as plus disease for this study.

dently by a second certified examiner and a second informed consent for cryotherapy was obtained, a randomization assignment was made via a phone call to the coordinating center. Most infants were enrolled shortly after birth and were followed at one of the 23 participating centers; however, additional patients meeting all eligibility requirements could be referred to study centers for late enrollment in the cryotherapy trial.

If both eyes developed threshold ROP, this was defined as a symmetric case and one eye was randomly assigned to receive cryotherapy, while the other eye would run its natural course and serve as a control. If disease in only one eye was confirmed to be at the threshold, only that eye would enter the randomized trial and would be randomized to either cryotherapy or no treatment (Fig 3). In asymmetric disease, the less severely affected fellow eye, in which ROP had not reached the threshold, was followed up by periodic examinations, and if ROP subsequently reached the threshold and the first eye had been randomized to "no cryotherapy," cryotherapy would be offered for the second eye, so that all infants who had two eyes with threshold ROP would have the opportunity to receive cryotherapy in one eye. The results of cryotherapy in the second eye in which ROP reached the threshold in asymmetric cases were not used in testing the benefit of cryotherapy. If disease in either eye had reached stage 4 (retinal detachment), the infant was considered monocular and declared ineligible for enrollment in the randomized cryotherapy trial.

Cryotherapy was carried out within 72 hours of detection of threshold ROP to minimize the risk of progression to stage 4 before treatment could be performed.

ELIGIBILITY DETERMINED

Consent Obtained
Asymmetric Disease Symmetric Disease

Randomize Patients Randomize Eyes

First Eye (or both eyes for symmetric disease)
Treat Not Treat Treat Not Treat

Second Eye
Progression To Eligibility
Not Treat Consider
Cryotherapy for the
Second Eye
CRYOTHERAPY TECHNIQUE

Although anesthesia was used in all cases, the physicians were given leeway in selecting from among topical anesthetic, local infiltration, local infiltration with sedation and/or paralysis, and general anesthesia. If general anesthesia was used, infants less than 44 weeks after conception were required to remain hospitalized and were connected to an apnea monitor for at least 24 hours postoperatively. If local anesthesia was used, a neonatologist was in attendance.

In many cases, no conjunctival incision was required, but when it was, a sterile field was established, and a scissors incision was made between the rectus muscles. While viewing the peripheral retina through a binocular indirect ophthalmoscope, the cryotherapist began the treatment with a row of applications at the ora serrata, followed by more posterior applications. Cryotherapy applications were made with a standard retinal probe, pediatric probe, or cataract probe, and were contiguous and single, rather than repeated and overlapping. The end point for each freeze was sudden whitening of the retina. A freeze time of 2 to 3 s was usually enough to produce the necessary appearance. As therapy continued the intraocular pressure would decrease, usually making it possible to reach the anterior edge of the fibrovascular ridge even if it was posterior to the retinal equator. The cryoprobe was completely withdrawn from the fornices at intervals of not more than five minutes to avoid any prolonged ocular hypertension and compromise of central retinal arterial flow. Cryotherapy was carried out until the entire anterior avascular retina had been treated back to the anterior edge of the ridge. This normally involved the entire circumference of the far peripheral retina and required an average of approximately 50 separate treatment spots (Table 1). All avascular retina anterior to the ridge was treated. Treatment did not extend posterior to the ridge, nor anteriorly into the pars plana. The funduscopic appearance of an ideal pattern of cryotherapy applications is indicated in Fig 4. In many cases, treatment was technically difficult and time-consuming. It was not rushed, and the eye was manipulated as gently as possible.

When a vitreous hemorrhage obscured the avascular zone, treatment was stopped because ophthalmoscopic monitoring of the treatment was impossible, and added manipulation might aggravate the bleeding. At least 24 hours later, if the hemorrhage cleared enough to allow it, cryotherapy was completed to the extent possible.

If cyanosis, bradycardia, or other systemic reactions occurred, the surgeon would remove the cryoprobe from the globe until the neonatologist and/or anesthesiologist had taken appropriate measures to remedy the situation and had given permission to proceed. If, during the course of cryotherapy, the child's condition became too unstable medically, the treatment session was terminated. The best medical judgment of the neonatologist and ophthalmologist was needed in determining whether to finish the treatment.

Postoperatively, one drop of 2% homatropine

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Randomized Patients (N = 291)</th>
<th>Patients With 3-mo Outcome Evaluation (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born in the study hospital (%)</td>
<td>64.9</td>
<td>64.5</td>
</tr>
<tr>
<td>Male (%)</td>
<td>51.5</td>
<td>52.9</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>69.1</td>
<td>68.0</td>
</tr>
<tr>
<td>Black</td>
<td>18.6</td>
<td>20.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Other</td>
<td>4.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Mean (±SD) birth wt (g)</td>
<td>800.05 ± 165.21</td>
<td>801.07 ± 170.64</td>
</tr>
<tr>
<td>Mean (±SD) gestational age (wk)</td>
<td>26.33 ± 1.85</td>
<td>26.37 ± 1.87</td>
</tr>
<tr>
<td>Multiple birth (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>77.3</td>
<td>74.4</td>
</tr>
<tr>
<td>Twins</td>
<td>21.7</td>
<td>24.4</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean (±SD) chronologic age at randomization (wk [range])</td>
<td>11.33 ± 2.40 (6.57 ± 23.86)</td>
<td>11.41 ± 2.56 (6.71 ± 23.86)</td>
</tr>
<tr>
<td>Mean (±SD) No. of cryotherapy applications</td>
<td>50.7 ± 24.6</td>
<td>52.0 ± 25.3</td>
</tr>
<tr>
<td>Mean (±SD) wt at cryotherapy (g)</td>
<td>1,826.43 ± 477.62</td>
<td>1,832.53 ± 522.78</td>
</tr>
<tr>
<td>Patients with symmetric disease (%)</td>
<td>82.5</td>
<td>80.8</td>
</tr>
</tbody>
</table>
hydrobromide or 0.25% scopolamine hydrobromide was instilled once or twice a day in both eyes through at least the fifth postoperative day. If the conjunctiva was opened, bacitracin zinc-polymixin B sulfate ointment (Polysporin) was instilled twice daily for three days. No steroid-containing medications were used.

If the eye that received cryotherapy was swollen shut for more than 24 hours, the opposite eye was occluded in an attempt to provide prophylaxis against amblyopia. The occlusive patch on the opposite eye was applied within 24 hours of the time it was noted that the eye that was operated on remained swollen shut and was left on until that eye reopened.

Both eyes of the treated infant were examined externally by an investigator within 72 hours of cryotherapy. At seven days after treatment the correct protocol management of each eye was verified through fundus examination by an examiner other than the primary cryotherapist. If a second cryotherapy session was needed, it was scheduled to be performed within 17 days after the first treatment. The sole indications for re-treatment included the presence of untreated (skipped) areas and the persistence of plus disease in association with either of the following characteristics: (1) segmental shallow retinal detachment (suggesting continued adjacent disease activity) in the areas skipped or (2) progression of extraretinal fibrovascular proliferation (increasing floridity of the ridge) contiguous with a skipped area. When re-treatment was performed, cryotherapy applications were made only to previously untreated avascular retina in sectors of continued activity.

OUTCOME

At 3 and 12 months after randomization, a detailed fundus examination was carried out independently by two investigators, and stereo photographs of the posterior pole and anterior segment of each study eye were taken.

The primary outcome for eyes in this clinical trial was derived from the masked assessment of these photographs, and a fundus photograph reading center was established for this purpose. Details of the photography protocol and the grading system will be published separately. Essentially, objective evidence was sought for the presence or absence of (1) a retinal fold involving the macula; (2) a retinal detachment involving zone 1 of the posterior pole; or (3) retrolental tissue or "mass." These anatomic features of abnormality were chosen with the expectation that eyes with unfavorable outcomes will have poor visual acuity. Although additional details such as macular ectopia were noted, at least one of the three features described above was necessary to classify an eye as having an "unfavorable" outcome. All eyes with other fundus appearances were classified as having a "favorable outcome." The photograph graders were unaware of whether an eye had received cryotherapy or whether any two eyes being graded belonged to the same infant.

SAMPLE SIZE

The sample size for our study was determined by specifying that there should be an 80% chance of detecting a 35% reduction in the risk of unfavorable outcome should cryotherapy prove beneficial. The risk of unfavorable outcome in untreated threshold eyes was believed to be 30% to 50%, and the lower limit was used in sample size calculations. The statistical test was chosen so that the type I error (α) was 0.05. With the assumption that 80% of infants would have symmetric disease, it was calculated that 300 infants would be needed to accomplish the study.

STATISTICAL ANALYSIS

Baseline characteristics of the study population were tabulated to describe the population of infants in the study. A combined analysis of the paired-sample data from infants with symmetric disease and the independent-sample data from infants with asymmetric disease was performed using a Mantel-Haenszel test. This provided a statistical test to compare the treated and control eyes at 3 months after randomization. From the outset, consideration was given to early termination of the trial should the data and
safety monitoring committee judge that the results warranted it. The results of the trial were reviewed every 6 months by this committee, which was composed of members with no other affiliation with the study. In addition to the statistical analyses previously described, the results were monitored using conditional power (stochastic curtailment).19,20

RESULTS

As of Oct 31, 1987, there were 9,356 infants of very low birth weight (weighing <1,251 g at birth) logged in at the participating centers. Many of these infants (2,668) did not survive to 28 days of age and hence were not included in any further evaluation for development of ROP. Forty-one infants were excluded from further study because of a fatal anomaly that would probably prevent long-term follow-up of the infant. Infants were also excluded if they had any eye anomaly that could confound results or make it difficult to study the future course of ROP, should it develop. An additional 2,785 infants were ineligible for study because they were either transferred to a non-participating hospital before 28 days of life or because informed consent was refused.

The remaining 3,862 infants who survived 28 days from birth and who otherwise met all eligibility requirements were followed up according to the study procedure to identify those who developed ROP.

During the course of the cryotherapy trial a total of 291 infants were randomized. For the 3-month outcome evaluation, the follow-up rate is 96%. At this writing, 172 of these infants had completed their 3-month outcome evaluation. The results in the present report are restricted to the 3-month outcome evaluation in these 172 infants, with only brief mention of the evaluation of outcome for 45 of these infants at 12 months after randomization. Table 1 shows a comparison of baseline characteristics of those infants for whom a 3-month outcome was available at this writing, compared with the entire group of 291 infants who were enrolled in the trial. Overall, there was a marked similarity in the general characteristics of these two groups. The total randomized population will be the subject of a later report.

Infants with symmetric and asymmetric ROP were randomized separately according to the design of the trial. Table 1 shows that approximately 82% of the infants had symmetric disease. The majority of infants (64.9%) were born in hospitals participating in the study. The number of female and male infants reaching eligibility for randomization was virtually identical (51.5% male). The study group was 69.1% white and 18.6% black. According to the study protocol, infant birth weight eligibility was restricted to less than 1,251 g; the infants who developed threshold ROP had an average birth weight of 800 g.

The subgroup of 172 infants included in this report had an average birth weight of 801 g. Cryotherapy was performed an average of 11.4 weeks after delivery (range, 6.7 to 23.9 weeks) and required a mean of 52 cryotherapy applications per eye (SD = 25). There were 11 cases in which a reapplication of cryotherapy was required.

The randomization procedure used to assign eyes to either cryotherapy or no treatment produced comparable groups of eyes with regard to severity of disease. There was an average of 9.6 clock hours of disease present at randomization in both the treated and untreated eyes. In the treated group 7.6% of eyes had zone 1 disease, and in the untreated eyes 5.9% of eyes had zone 1 disease.

The results of the 3-month outcome based on the fundus photography evaluations are presented in Table 2. There was an overall 49.3% reduction in the unfavorable outcome rate at three months in the treated eyes vs the untreated eyes (21.8% compared with 43.0%, with a corresponding $\chi^2$ of 20.5 and $P < .00001$). The primary reasons for classifying outcome as unfavorable

| TABLE 2. Photographic Evaluation of Outcome at 3 Months After Treatment With Cryotherapy |
|--------------------------------------------------|--------------------------------------------------|-----------------|-----------------|
| Treated Eye                                     | Untreated Eye                                    | $\chi^2$     | $P$             |
| No.     | % Unfavorable | No.     | % Unfavorable |                |                |
| Symmetric cases                                | 137*     | 24.1   | 136*     | 45.6   | 19.6†       | .00001         |
| Asymmetric cases                               | 19       | 5.3    | 13†      | 15.4   | 0.9        | .34             |
| Total                                           | 156      | 21.8   | 149      | 43.0   | 20.5†      | <.00001         |

* Less than 139 because of the inability to grade photographs.
† Based on the discordant pairs (34 in which outcome in the treated eye was favorable while in the untreated eye it was unfavorable, and six in which outcome in the untreated eye was favorable while in the treated eye it was unfavorable).
‡ Less than 14 because of the inability to grade photographs.
were a retinal fold involving the macula, retinal detachment involving the posterior pole, or a total retrolental mass.

In the subgroup of infants with symmetric disease, in which one eye was treated and the other eye served as a control eye, 45.6% of untreated eyes showed an unfavorable outcome, and 24.1% of treated eyes showed an unfavorable outcome. When asymmetric disease was present, 15.4% of the infants in the untreated group had unfavorable results, and 24.1% with unfavorable outcome in treated eyes compared with the group of untreated eyes. Unfavorable outcome occurred in only 5.3% of the treated eyes in infants with asymmetric disease, compared with the 24.1% with unfavorable outcome in treated eyes of infants with symmetric disease. In untreated eyes, 15.4% of infants with asymmetric disease had an unfavorable outcome, whereas 45.6% of infants with symmetric disease that had an unfavorable outcome.

In addition to the evaluation of photographs of the posterior pole, separate clinical examinations were done for each infant by two study physicians 3 months after randomization. The results were recorded so that they could be compared with the results of the photographic evaluation. This was a secondary evaluation, since the examiners could usually tell which eye had received cryotherapy. The results of these clinical evaluations are given in Table 3, which shows the 48.5% reduction in the rate of unfavorable outcome in the treated eyes compared with the group of untreated eyes (23.5% to 45.6%).

The results in Table 3 agree closely with those shown in Table 2, particularly for infants with symmetric disease. In both Tables 2 and 3, the data show that there is a clear benefit from cryotherapy at 3 months after treatment. The benefit was a reduction of approximately 50% (95% confidence limits, 32% to 62%) in the rate of unfavorable outcomes.

In addition to data presented in Tables 2 and 3, other overall issues were considered in the decision to provide an interim report of the results and to terminate further randomization. Two primary subjects of this deliberation were the likelihood that the favorable results of cryotherapy, as demonstrated in Tables 2 and 3, would continue to prevail if the study went to its completion, and the question of whether the results at 3 months, although striking, would lead to essentially the same conclusion about cryotherapy at the second, 12-month evaluation.

An evaluation of these issues using the 3-month data included the calculation of the probability (conditional power) that the study would ultimately lead to essentially the same conclusion, even if there were no expected benefit whatsoever from cryotherapy during the remaining portion of the trial. This procedure for monitoring the accumulating results of a trial can lead to termination of a trial when there is strong evidence of benefit. It is conservative in that it seldom leads to stopping a long-term trial very early.

Enrollment in this cryotherapy trial was stopped on Jan 22, 1988, and all principal investigators were informed on Jan 25, 1988. If the study had continued to randomize infants to the projected stopping date, there would have been approximately 280 infants with symmetric disease participating in the cryotherapy trial. This would likely have led to an additional 45 infants with symmetric disease in which the 3-month outcome would show that one eye has a favorable outcome and the other eye has an unfavorable outcome. These 45 infants would be added to the 40 infants in whom a discrepancy in anatomical findings already exists. The conditional power is 94%, indicating that it is highly likely that the benefit from cryotherapy can be reached early, without

<table>
<thead>
<tr>
<th>TABLE 3. Physician’s Summary Diagnosis of Outcome at 3 Months After Treatment With Cryotherapy</th>
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<tbody>
<tr>
<td>Treated Eye</td>
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<tr>
<td>-------------</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Symmetric cases</td>
</tr>
<tr>
<td>Asymmetric cases</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

* Less than 139 because two infants were not examined and no information was available on three infants.
† Based on discordant pairs (36 in which outcome in the treated eye was favorable while in the untreated eye it was unfavorable, and three in which outcome in the untreated eye was favorable while in the treated eye it was unfavorable).
‡ Less than 14 because no information was available on one infant.
Data were reviewed for the 45 infants who had also already completed the 12-month examination. At the time of the present report there were 14 infants with an interocular difference in outcome. Of these 14 infants, 13 had a favorable outcome in the treated eye and an unfavorable outcome in the untreated eye, whereas only one infant had a favorable outcome in the untreated eye and an unfavorable outcome in the treated eye. These early results of the 12-month outcome assessment are consistent with those at 3 months shown in Table 2.

Further calculations of conditional power, allowing for the differential outcome between treated and untreated eyes that exists at three months (Table 2), indicate that a similar pattern is likely to be maintained at 12 months. Further relevant clinical details regarding the 12-month results, including visual outcome, will be forthcoming as the infants who are currently enrolled in the present study are followed up through the 12-month outcome assessment.

Intraoperative ocular and/or systemic complications occurring during cryotherapy were recorded prospectively, and more frequent ones are shown in Table 4. Conjunctival or subconjunctival hematoma was observed in 10.2% of the cases; unintended conjunctival laceration was seen in 5.1% of patients; and retinal, preretal, or vitreous hemorrhage was found in 19.1% of patients. The other ocular complications (1.3%) were proptosis secondary to xylocaine diffusion and dilatation of the tunica vasculosa lentis. Bradycardia or arrhythmia was reported in 8.9%, and acquired or increased cyanosis was seen in 1.9%. Other systemic complications (2.5%) included transient hypertension, transient hypotension, transient hypoxemia, and one case of temporary respiratory arrest that was probably due to the degree of anesthesia. No deaths from treatment occurred. Additional possible complications that were not found were closure of the central retinal artery, inadvertent freezing of the optic nerve or macula, eye muscle laceration or avulsion, perforation of the globe, orbital wall injury, aspiration, or seizures.

### COMMENT

The results shown in Tables 2 and 3 led the Data and Safety Monitoring Committee for the CRYO-ROP Study to recommend orderly termination of further randomization with continued follow-up of the infants currently in the study and preparation of this interim report of the results of the CRYO-ROP Study before the intended close of enrollment on June 30, 1988.

We wish to emphasize that, at this writing, the follow-up of these patients was incomplete and is continuing. Many details may yet be revealed that could affect the clinician's judgment as to the appropriateness of cryotherapy for a particular eye. These data, at least until 3 months after treatment, indicate that cryotherapy for one eye is safe and effective for the patients described. Despite this benefit, it is worth remembering that unfavorable outcomes did occur in eyes that received cryotherapy (24.1%). There are insufficient long-term data at present for us to reach a conclusion on the wisdom of routinely applying cryotherapy to both eyes of a patient with bilateral threshold ROP, or of applying cryotherapy in any different pattern than that used in this trial, or of applying it to patients with less severe disease. Subsequent data collection should lead to prognostic indicators for patients with ROP at subthreshold levels, which will be necessary to evaluate indications for earlier cryotherapy.

We recognize that the finding reported herein will affect ophthalmic management of some premature infants and that expectations of neonatologists will be altered by these findings. Neonatologists have long recognized the need to develop screening protocols for early eye examinations to determine a prognosis for vision. Now, however, neonatal intensive care units will require the services of an ophthalmologist who can examine the highest-risk infants (particularly those weighing <1,251 g at birth) beginning at 4 to 6 weeks of age. When the ROP reaches the threshold, immediate arrangements for cryotherapy will be needed. It should be noted that not

### TABLE 4. Complications During Cryotherapy (N = 157*)

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. (%) of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative ocular complications</td>
<td></td>
</tr>
<tr>
<td>Conjunctival or subconjunctival hematoma</td>
<td>16 (10.2)</td>
</tr>
<tr>
<td>Conjunctival laceration, unintended</td>
<td>8 (5.1)</td>
</tr>
<tr>
<td>Hemorrhage: retinal, preretal, vitreous</td>
<td>30 (19.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Systemic complications</td>
<td></td>
</tr>
<tr>
<td>Bradycardia or arrhythmia, including asystole</td>
<td>14 (8.9)</td>
</tr>
<tr>
<td>Acquired or increased cyanosis</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2.5)</td>
</tr>
</tbody>
</table>

* Less than 172 because of 14 asymmetric control eyes and one regressing asymmetric treated eye that did not receive cryotherapy (included as randomized, ie, treated, in all previous tables).
all ophthalmologists are experienced in examining or treating small premature infants. Intensive care nurseries where cryotherapy is not available should be capable of transferring selected patients to facilities where skilled evaluation and cryotherapy are obtainable. In many instances it will take time to establish a system for providing these therapeutic arrangements.

In conclusion, these data lead us to recommend cryotherapy for at least one eye of symmetric cases at the threshold. For the fellow eye in such cases and for the single eye at the threshold in asymmetric cases, the surgeon should use clinical judgment in the light of our findings. Further analysis of the accumulating data is expected to provide additional clinically important information.

ACKNOWLEDGMENTS

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Many ophthalmologists provided advice during the initial protocol development, and these are acknowledged in the CRYO-ROP Study procedure manual. Israel Goldberg, PhD, provided valuable advice during initial protocol development, and these are acknowledged in the CRYO-ROP Study procedure manual. Israel Goldberg, PhD, provided valuable advice during protocol development.

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Louisiana Center (New Orleans): Charity Hospital of New Orleans, Tulane Medical Center. Principal Investigator: Robert A. Gordon, MD; Coinvestigators: Carolyne Busch, BSN, W. Michael DeVoe, MD, James G. Diamond, MD, William L. Gill, MD, Donald R. May, MD, Jane E. Reynolds, MD, Frank Saucier, Thomas G. Storch, MD, Becky Thiele; Past Coinvestigators: Robert M. Lewen, MD, Kirby Miller, Nancy Raff.

Maryland Center (Baltimore): The Johns Hopkins Hospital, Francis Scott Key Medical Center. Principal Investigator: Serge de Bustros, MD; Coinvestigators: Alethia Alford, David G. Emmert, Terry W. George, RBP, Bert M. Glaser, MD, Janet Graeber, MD, Ronald G. Michels, MD, Michael Repka, MD.

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Ohio, Columbus Center: Columbus Children's Hospital, University Hospital. Principal Investigator: Gary L. Rogers, MD; Coinvestigators: Don L. Bremer, MD, Leandro Cordero, MD, Rae R. Fellows, MED, Nancy B. Hansen, MD, Alan D. Letson, MD, Richard E. McLeod, MD, Beverly Radcliffe, Sue Stephen, RN.

Oregon Center (Portland): The Oregon Health Sciences University, Emanuel Hospital, Good Samaritan Hospital. Principal Investigator: Earl A. Palmer, MD; Coinvestigators: Arthur A. Aaby, MD, Raul Banagale, MD, Mark Evans, Shawn Goodman, MD, Irvin Handelman, MD, Michael L. Klein, MD, Susan B. LaFrance, RN, John W. Reynolds, MD, Joseph Robertson, MD, Andrea C. Tongue, MD, Patrick Wallace.

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Study Headquarters, The Oregon Health Sciences University, Portland: Principal Investigator: Earl A. Palmer, MD; Administrative Coordinator: Cynthia L.
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