OUTCOME OF EYES DEVELOPING RETINAL DETACHMENT DURING THE EARLY TREATMENT FOR RETINOPATHY OF PREMATURETY STUDY (ETROP)

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Objective: To report the structural and visual outcomes of eyes in which retinal detachment developed from retinopathy of prematurity (ROP) in the Early Treatment of Retinopathy of Prematurity (ETROP) Study.

Method: Infants in the ETROP Study with bilateral high-risk prethreshold ROP had 1 eye randomized to early treatment, with the fellow eye managed conventionally. In infants with asymmetric disease, the eye with high-risk prethreshold ROP was randomized to early treatment or conventional management. When a retinal detachment was detected, observation or vitreoretinal surgery (ie, scleral buckling and/or vitrectomy) was provided at the discretion of the individual investigator. At 9 months corrected age, retinal examinations were performed and visual acuities were assessed by masked testers using grating acuity.

Results: The ETROP Study enrolled 401 patients with high-risk prethreshold ROP. Retinal detachments occurred in 89 eyes of 63 patients. Follow-up was available for 78 eyes of 56 patients. The detachments were bilateral in 21 patients (38%) and were classified as stage 4A in 30 eyes, stage 4B in 14 eyes, and stage 5 in 16 eyes. Detachments were not classified in 18 eyes. Twelve eyes of 11 patients were observed and 66 eyes of 52 patients underwent vitreoretinal surgery. Attachment of the macula at 9 months persisted or was achieved in 17 (30%) of 56 eyes after vitrectomy with or without scleral buckle, in 6 (60%) of 10 eyes after scleral buckle only, and in 2 (17%) of 12 eyes followed up without surgery. Favorable visual acuity (≥1.85 cycles/degree) was found in 13 (17%) of the 78 eyes. All 6 eyes that maintained normal visual acuity (≥3.70 cycles/degree) had a stage 4A detachment (1 of 6 managed by observation, 3 of 6 by scleral buckle, and 2 of 18 by vitrectomy). Eleven eyes with stage 5 detachment underwent vitreoretinal surgery, resulting in 6 with no light perception, 3 with light perception only, and 2 with detection of only the low vision card.

Conclusions: In the ETROP Study, the outcome of retinal detachment owing to ROP was generally poor. Vitreoretinal surgery for retinal detachment was associated with macular attachment in 16 of 48 eyes. Normal acuity was maintained after surgical repair of stage 4A retinal detachment in 5 (21%) of 24 eyes. Vitreoretinal surgery for stage 5 disease was associated with some structural successes but poor functional outcomes.

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RETIINAL ABLATION PERFORMED with cryotherapy or laser therapy improves the structural and functional outcomes of children with severe retinopathy of prematurity (ROP). However, such therapy does not always prevent progression of disease to retinal detachment. Without vitreoretinal surgery, the outcome for eyes with stages 4B and 5 retinal detachments is thought to be poor. Reports of nonrandomized case series have shown that scleral buckling and vitrectomy techniques can successfully reattach the retina of children with stages 4 and 5 retinal detachments. Some authors have noted that earlier treatment of severe retinal disease was associated with better structural outcomes. However, the visual results after such interventions have been disappointing. An exception has been the treatment of stage 4A detachments with scleral buckling or lens-sparing vitrectomy, where better structural and visual outcomes have been reported in case series.

The Early Treatment for Retinopathy of Prematurity (ETROP) Cooperative Group recently compared ablative therapy administered before reaching threshold with conventional management in a group of high-risk prethreshold eyes. High-risk eyes were identified using a multiple risk factor model. The investigators found that early treatment of eyes with high-risk prethreshold ROP significantly improved the structural and functional outcomes. However, progression to retinal detachment oc-
Premature infants with birth weights less than 1251 g who developed ROP were enrolled in the ETROP Study at 26 centers from October 1, 2000, through September 30, 2002. The study protocol was approved by the investigational review boards of each participating nursery, and written informed consent was obtained from parents and guardians for all study procedures. Details of the protocol have been previously published. In brief, eyes with a 15% or greater risk of an unfavorable outcome at 3 months corrected age were identified by a risk model analysis. Infants with symmetrical disease were randomized to early or conventional management. The study medical records of 401 randomized patients were reviewed for the presence of a retinal detachment or the performance of vitreoretinal surgery (Figure). Retinal detachment and/or vitreoretinal surgery was reported in 89 eyes of 63 patients. Among the 13 infants (14 eyes) who did not undergo surgery, 2 patients (1 eye of each) died before the 9-month outcome examination. Vitreoretinal surgery was performed in 75 eyes of 57 patients. Among those who underwent surgery, 4 patients (7 eyes) died before the 9-month outcome examination, and 1 patient (2 eyes) did not have a visual acuity outcome reported (retina totally attached in each eye). Thus, a 9-month outcome examination was completed for 66 eyes of 52 patients who underwent vitreoretinal surgery and 12 eyes of 11 patients who were observed. Seven of these patients had bilateral detachments, with 1 eye treated surgically, whereas the fellow eye was observed, leaving a cohort of 56 patients. The treatment selection was not randomized, and the numbers were too small to allow a comparison.

The 56 patients had a mean birth weight of 706 g and a mean gestational age of 25.0 weeks. The baseline demographic characteristics of the 3 treatment subgroups are listed in Table 1. The groups did not differ in any of the conditions assessed.

**Figure.** Patient flow diagram. Asterisk indicates 7 patients with 1 eye in each group.

Visual acuity testing at 9 months corrected age was performed by study-certified testers who were masked to the infant’s eye treatment. The testers assessed grating acuity using previously described methods. The results of grating visual acuity assessment were categorized as favorable (normal [≥3.70 cycles/degree] and below normal [1.85 to <3.70 cycles/degree]), poor (<1.85 cycles/degree), low vision (detection of only the 2.2-cm-wide stripes of the Teller low vision card at any distance), light perception only, or no light perception.

**METHODS**

Premature infants with birth weights less than 1251 g who developed ROP were enrolled in the ETROP Study at 26 centers from October 1, 2000, through September 30, 2002. The study protocol was approved by the investigational review boards of each participating nursery, and written informed consent was obtained from parents and guardians for all study procedures. Details of the protocol have been previously published. In brief, eyes with a 15% or greater risk of an unfavorable outcome at 3 months corrected age were identified by a risk model analysis. Infants with symmetrical disease were randomized to early or conventional management. The study medical records of 401 randomized patients were reviewed for the presence of a retinal detachment or the performance of vitreoretinal surgery (Figure). Retinal detachment and/or vitreoretinal surgery was reported in 89 eyes of 63 patients. Among the 13 infants (14 eyes) who did not undergo surgery, 2 patients (1 eye of each) died before the 9-month outcome examination. Vitreoretinal surgery was performed in 75 eyes of 57 patients. Among those who underwent surgery, 4 patients (7 eyes) died before the 9-month outcome examination, and 1 patient (2 eyes) did not have a visual acuity outcome reported (retina totally attached in each eye). Thus, a 9-month outcome examination was completed for 66 eyes of 52 patients who underwent vitreoretinal surgery and 12 eyes of 11 patients who were observed. Seven of these patients had bilateral detachments, with 1 eye treated surgically, whereas the fellow eye was observed, leaving a cohort of 56 patients. The treatment selection was not randomized, and the numbers were too small to allow a comparison.

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**PROCEDURES**

The indications for and timing of technique of vitreoretinal surgery for retinal detachment were not specified by the ETROP protocol. For the purposes of this report, vitreoretinal surgery includes vitrectomy, scleral buckling, or both. The vitreoretinal surgeons were located at ETROP clinical centers and at nonparticipating facilities. The procedures were performed at the discretion of the investigator. A 6-month study form documenting the ocular status was completed before the surgery in most cases (73%).

Study-certified ophthalmologists conducted retinal examinations at 6 and 9 months corrected age. The status of the retina was categorized by the study ophthalmologist as normal, straightened temporal retinal vessels, macular ectopia, partial retinal detachment not including the macula (stage 4A), partial retinal detachment including the macula (stage 4B), and total retinal detachment (stage 5). At the 9-month examination, the condition of some retinas could not be graded because of cataract or vitreous hemorrhage. Echography was used at the discretion of the examining physician to supplement the findings of ophthalmoscopy but was not required.
these characteristics. The retinal detachment was bilateral in 21 (38%) of the patients. The 78 retinal detachments were classified as stage 4A in 30 eyes, stage 4B in 14 eyes, and stage 5 in 16 eyes. Detachments were not classified in 18 eyes. Table 2 provides a breakdown subdivided by treatment. Twelve eyes were observed, 10 eyes underwent scleral buckling only, and 56 underwent vitrectomy (5 with scleral buckling before the vitrectomy, and 7 with simultaneous scleral buckling). The median postmenstrual age (gestational age plus time after birth) at the time of the first vitreoretinal surgery was 41.9 weeks (range, 37.4-76.0 weeks), whereas...
the median chronological age was 17.0 weeks (range, 11.9-62.5 weeks). This treatment occurred a median of 6.0 weeks after ablative therapy (the value excludes 3 eyes that were treated with ablative therapy at the time of the scleral buckling or vitrectomy).

**STRUCTURAL OUTCOME**

At the 9-month examination, overall attachment of the macula was noted in 2 (17%) of 12 eyes after observation, in 6 (60%) of 10 eyes after scleral buckle only, and in 17 (30%) of 56 eyes after vitrectomy with or without scleral buckle (Table 2). The detachments were not classified in 18 eyes before vitreoretinal surgery, and these eyes are excluded from this subgroup analysis on the basis of preoperative stage.

Observation of 6 eyes with stage 4A detachment and without vitreoretinal surgery found that 2 eyes improved, whereas 4 worsened from the 6-month to the 9-month examinations. Observation of 2 eyes with stage 4B detachment found that both remained stage 4B at 9 months, whereas observation of stage 5 eyes found that all 4 eyes remained totally detached (Table 2).

In the group that underwent scleral buckling only, macular attachment that was present before scleral buckling was successfully maintained for 5 of 6 eyes with stage 4A detachment, whereas the other eye retained some extramacular attachment (Table 2). Two of 3 eyes with stage 4B or stage 5 detachment had some portion of retina attached after scleral buckling.

The eyes that underwent vitreoretinal surgery were sub-divided by the International Classification of Retinopathy of Prematurity system of the retinal detachment at the time of the first vitreoretinal procedure (Table 2). After vitreoretinal surgery, an attached macula was seen in 5 (28%) of 18 eyes with stage 4A detachment before surgery, 5 (50%) of 10 with stage 4B detachment before surgery, and 2 (18%) of 11 with stage 5 detachment before surgery. Vitreoretinal surgery was associated with attachment of a portion of the retina at the 9-month examination for 6 (50%) of 12 eyes with stage 4B detachment before surgery, whereas it reattached some portion of the retina in 5 (42%) of 12 eyes with stage 5 detachment before surgery (Table 2).

**FUNCTIONAL OUTCOME**

Overall, favorable visual acuity was found in 13 (17%) of the 78 eyes, with 6 eyes having visual acuity in the normal range. Favorable visual outcomes were seen in 1 (8%) of 12 eyes after observation, in 4 (40%) of 10 after scleral buckling only, and in 8 (14%) of 56 eyes after vitrectomy with or without scleral buckle (Table 2). Of these 13 eyes with favorable visual acuity, 9 were associated with stage 4A detachment before surgery or at the 6-month examination, 1 with stage 4B detachment, and none with stage 5 detachment. In 3 eyes, the preoperative retinal detachment was not classified (no examination or drawing before surgery).

For the 12 eyes with stage 5 detachment that underwent surgery, there were no eyes with favorable or poor visual outcomes. Two had detection only of the low vision card, 4 had light perception only, and 6 had no light perception. Among the 4 eyes with stage 5 detachment that were observed without surgery, all had no light perception at the 9-month examination. The small sample sizes, varied nature of the detachments, and differing surgical indications and timing between centers do not allow comparison between the 3 treatment approaches or analysis of the impact of scleral buckling when performed in conjunction with vitrectomy.
STRUCTURE AND FUNCTION AFTER VITREORETINAL SURGERY

The impact of the structural outcome on function is shown in Table 4 for the 66 eyes that had vitreoretinal surgery. Total retinal attachment was a good indicator of measurable visual acuity at the 9-month examination. Of the 21 eyes in which the retinas were totally attached, favorable Teller visual acuity was found in 9, whereas 8 eyes had light perception only or no light perception. Attachment of some portion of the retina allowed at least poor visual acuity in 16 eyes, whereas less than poor visual acuity was found in 20 eyes. Of the 20 eyes with total retinal detachment at the 9-month examination, 2 had low vision, and 18 had no light perception.

<table>
<thead>
<tr>
<th>Visual Outcome at 9 Months</th>
<th>Structural Outcome at 9 Months</th>
</tr>
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<tbody>
<tr>
<td>FTV</td>
<td>Attached</td>
</tr>
<tr>
<td>Poor Teller</td>
<td>(Stage 4A)</td>
</tr>
<tr>
<td>Low vision</td>
<td>Attached</td>
</tr>
<tr>
<td>Light perception</td>
<td>Attached</td>
</tr>
<tr>
<td>No light perception</td>
<td>Attached</td>
</tr>
<tr>
<td>Attached</td>
<td>9</td>
</tr>
<tr>
<td>MAA</td>
<td>2</td>
</tr>
<tr>
<td>Some retina</td>
<td>1</td>
</tr>
<tr>
<td>Unable to Grade</td>
<td>2</td>
</tr>
<tr>
<td>Total Eyes, No. (%)</td>
<td>12 (18)</td>
</tr>
</tbody>
</table>

Table 4. Correlation of Structure and Function for Eyes Undergoing Vitreoretinal Surgery

Abbreviation: RD, retinal detachment.
*Ellipses indicate none.

COMMENT

Early retinal ablative treatment of high-risk prethreshold ROP has been shown to reduce the rate of unfavorable structural and functional outcomes.1 However, retinal detachment still occurred in 89 (12%) of 718 randomized eyes before 9 months corrected age. Outcome results were available for 78 (88%) of these eyes. Infants with a retinal detachment in the ETROP Study were observed or underwent vitreoretinal surgery at the discretion of the individual investigator. There was no study protocol for treatment of patients with a retinal detachment.

Most eyes (66 [85%] of 78) with detached retinas underwent vitreoretinal surgery in an attempt to reattach the retina or prevent progressive detachment. The first surgical procedure was performed at a median of 41.9 postmenstrual weeks. Observation, scleral buckling, and vitrectomy (with or without scleral buckling) for partial retinal detachment were associated with maintained attachment of the macula in 17%, 60%, and 30% of eyes, respectively. No conclusion should be drawn about the relative merits of these approaches and procedures, because the surgical indications were not standardized and the eyes were not randomized.

Results of the ETROP Study after retinal detachment cannot be compared with those of the Cryotherapy for Retinopathy of Prematurity Cooperative Group Study, because that study’s protocol did not permit vitreoretinal surgery until there was a total retinal detachment.17 The results of scleral buckling for partial detachment in the present study are consistent with those of previous studies,5,6,9,18-20 whose authors reported reduced progression with retinal attachment rates of 46.4% to 75%. However, those studies used differing definitions for success. It is also likely that in the ETROP Study, vitrectomy may have been used for some of the cases that might have been treated with scleral buckling in the earlier case series.

Hinz and colleagues9 have suggested that scleral buckling performed at an earlier stage of detachment, typically when the detachment is only peripheral and when the ROP remains active and has not yet involuted, could prevent progression of the retinal detachment or lead to reattachment. Other investigators have similarly suggested earlier vitrectomy for stage 4A detachment to further improve the outcome by preventing progression to more extensive detachments. Capone and Trese10 reported that a lens-sparing vitrectomy for stage 4A detachment in 40 eyes resulted in a complete retinal attachment in 90%, whereas Hubbard and colleagues11 reported 84% reattachment after vitrectomy in a series of 25 patients. In the ETROP Study, vitrectomy for stage 4A detachment was not as successful as in those reports, with persistent attachment of the macula in only 5 (28%) of 18 eyes. The results observed in the ETROP Study may vary because of differing indications, timing of surgery, or experience of the vitreoretinal surgeons. In addition, the ETROP Study forms were completed before anesthesia, possibly leading to the misclassification of some children as having 4A detachment when they actually had macular detachment (stage 4B detachment).

The initial vitreoretinal surgery in the ETROP Study eyes was performed at a median postmenstrual age of 41.9 weeks. This seems to be about the same age for the recently reported case series of scleral buckling6,9,18,19 and vitrectomy.10

The structural and visual outcomes after observation of an ROP-associated retinal detachment noted at 6 months were poor. Among the 8 eyes with partial detachment observed at 6 months (6 with and 2 without the macula attached), only 2 were completely reattached at 9 months and only 1 of these had favorable visual acuity. Thus spontaneous reattachment of a retinal detachment with or without restoration of useful vision is very unusual. This confirms the findings of the Cryotherapy for ROP Study, which found a generally poor visual outcome with observation of a partial detachment7 and no useful vision with observation or vitrectomy for stage 5 detachment.8
Scleral buckling for stage 4A detachment in the ETROP Study was associated with measurable grating visual acuity in all 6 cases, with 4 in the favorable range. Scleral buckling was not successful in retaining measurable visual acuity for eyes with stage 4B or stage 5 detachment in this study. This differs from some earlier reports. Greven and Tasman\(^2\) found that 4 of 10 eyes with stage 4B or 5 detachment treated with scleral buckling had 20/400 or better visual acuity. Noorily and colleagues\(^3\) had fixation- and-following visual acuities in 3 of 15 consecutive eyes with stage 4B detachment treated with scleral buckling. Ricci and colleagues\(^4\) found detectable vision in 13 of 28 eyes with stage 4 detachment after scleral buckling. However, quantitative visual acuity assessment was possible in only 6 of their 10 eyes. These differences in outcome likely result from the small sample sizes and possibly differences in classification of retinal detachment.

Vitrectomy was associated with favorable visual acuity in 4 (22%) of 18 eyes with stage 4A detachment and 1 (10%) of 10 with 4B detachment. Capone and Trese\(^5\) were able to maintain fixation behavior in 90% of the eyes with stage 4A detachment treated with lens-sparing vitrectomy. However, fixation behavior cannot be reliably quantified, and it tends to overestimate optotype acuity, thereby making it impossible to compare these findings with those in the ETROP Study eyes.\(^6\) Premer and colleagues\(^7\) used Teller cards or Allen pictures in a non-standardized fashion to determine visual acuity at a mean of 3.51 years after vitrectomy for stage 4A detachment. They reported a mean visual acuity of 20/58 in 23 of 45 eyes that could undergo testing. Optotype visual acuity data from the ETROP eyes are being collected at 4, 5, and 6 years of age and will be reported when available.

Vitrectomy for the 11 eyes with stage 5 detachment in the ETROP Study produced no eyes with favorable visual acuity, although there were 2 eyes with the lowest level of pattern vision (low vision card) and 3 with light perception only. Similar visual outcomes were described after advanced retinal surgery for eyes with stage 5 detachment enrolled in the Cryotherapy for ROP Study conducted from 1986 to 1987.\(^8,9\) Those authors reported that only 2 of 72 eyes that underwent vitrectomy achieved any pattern vision and that was at the lowest level, the low vision card. However, by 5½ years of age, those eyes were also blind. Trese and Droste,\(^10\) in a retrospective case series from 1998, reported more optimistic results with vitrectomy. In a single-center series, those authors operated on 11 eyes with stage 5 retinal detachment (1982–1995). Three children were lost to follow-up. Of the remaining 8 children, 4 had no light perception, 2 had light perception, and 2 had pattern vision (20/800 and 20/1900).\(^11\)

Visual function at the 9-month examination was related to the final retinal structure. In the ETROP Study, 21 (32%) of 66 eyes that underwent vitreoretinal surgery had total retinal attachment, although only 12 (18%) of 66 had favorable visual acuity. The reduced visual acuity may be due to retinal damage from the ROP-associated detachment, but may also be related to damage during surgery, optic neuropathy, and cortical visual impairment in these infants.\(^12\) In general, the eyes with the greater extent of retinal attachment, especially when the posterior pole was normal, had better visual acuity. These data suggest that the objective in the management of ROP should be a normal posterior pole with complete retinal attachment.

The results from the ETROP Study may represent a more generalizable outcome of this disease than that found in highly specialized single-center case series. Follow-up was available for nearly all of the eyes with a retinal detachment through 9 months corrected age in the ETROP Study. Structural assessments in some cases were performed by clinicians who had not performed the vitreoretinal surgery. Most importantly, certified traveling acuity testers masked to the patient’s treatment(s) performed the visual acuity testing.

The findings of this study are limited by a number of factors. First, the relatively small number of patients in each subgroup prevents statistical comparison. Second, the classification of the retinal detachment in 18 eyes (23%) was not recorded on study forms before surgery, and for the remaining patients the classification was limited to only 3 stages of detachment (4A, 4B, and 5). Third, the natural history of the eyes similar to those undergoing operation was unknown, making assessment of the effectiveness of the treatment impossible. Fourth, there was no standardized protocol for the indications, timing, and techniques of vitreoretinal surgery. For example, 5 patients underwent scleral buckling first, followed by vitrectomy, and 7 underwent simultaneous scleral buckling and vitrectomy. Fifth, the surgical outcomes could be affected by the differing experience of the surgeons performing the scleral buckling and vitrectomy. Sixth, the treatment subgroups were not balanced for disease severity. Clinicians in this study recommended surgery for differing levels of severity of ROP. For instance, study physicians performed scleral buckling and vitrectomy for stage 4A disease in some children, whereas in other children such surgery was not recommended even for stage 5 disease. In some cases surgery could not be performed because of other medical issues, further delaying the intervention. Seventh, the rate of retinal reattachment may not yet be stable at this early follow-up time, as retinas may still reattach or detach. In addition, the visual acuity results at the 9-month outcome examination, in some cases just weeks after the retinal surgery, should be considered preliminary. Some patients may show improvement of visual acuity with further follow-up and cognitive development, whereas others may show deterioration.

Follow-up assessment of eyes in the ETROP Study at 6 months corrected age found a retinal detachment in 12% of randomized eyes. Among the 66 eyes that underwent vitreoretinal surgery, 21 (32%) had total retinal attachment at the 9-month outcome examination, although only 12 (18%) had favorable visual acuity. Scleral buckling only was performed in 10 eyes, with at least some retina attached in 8 eyes and favorable visual acuity noted in 4. Vitrectomy was associated with a 28% (5/18) rate of retinal macular attachment for stage 4A detachment, with favorable visual acuity noted in 4 (22%) of 18. Four of 11 eyes with total retinal detachment (stage 5) were at least partially reattached after vitrectomy. However, for these 11 eyes, only 2 had low-level pattern vision and
3 had light perception only. These data highlight the severe visual impact of retinal detachment in ROP, the difficulty achieving total retinal attachment, and the gap between structure and function after structural repair of retinal detachment. This study confirms that there remains an urgent need for clinical trials studying the management of retinal detachments associated with ROP to provide clinicians with guidance about the timing and technique of surgery. Additional research into the medical management of the cicatrization process to prevent progression to retinal detachment is needed.

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