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Arch Ophthalmol. Author manuscript; available in PMC 2015 May 01.

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Published in final edited form as:

Arch Ophthalmol. 2011 September ; 129(9): 1175–1179. doi:10.1001/archophthalmol.2011.229.

Outcome of Eyes Developing Retinal Detachment during the Early Treatment for ROP Study (ETROP)

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Abstract

PURPOSE—To describe the structural and visual outcomes at age 6 years of retinal detachment (RD) from retinopathy of prematurity (ROP) in the Early Treatment of ROP (ETROP) study.

METHODS—Prospective multi-center non-randomized series of infants with high-risk prethreshold ROP who developed an RD by 6 months corrected age managed with observation or vitreoretinal surgery at investigator discretion.

RESULTS—401 subjects were enrolled in ETROP. RD occurred in 89 eyes of 63 subjects. Follow-up at age 6 years was available for 70 eyes (79%) of 49 subjects. The RDs were stage 4A in 28 eyes (40%), stage 4B in 14(20%), stage 5 in 13(19%), and not classified in 15(21%). The macula was attached in 17 of 50 eyes (34%) following vitrectomy with or without scleral buckle, in 6 of 9(67%) following scleral buckle only, and in 2 of 11 eyes (18%) observed. An attached macula at 6 years of age following vitreoretinal surgery was present in 5 of 16 eyes with stage 4A(31%), 6 of 10 with stage 4B(60%) and 0 of 10 with stage 5.

Favorable visual acuity (> 20/200) was found in 6 of 70 eyes (8.6%); 5 had stage 4A, one not classified. Ten stage 5 eyes underwent vitreoretinal surgery; one retained light perception, 8 were blind and 1 was untestable.

CONCLUSION—Macular attachment was achieved in about one-third of eyes with RD and favorable visual acuity for some eyes with stage 4A. These data confirm the difficulty of obtaining useful vision once ROP has progressed to detachment.

INTRODUCTION

Retinal ablation improves the structural and functional outcomes of children with severe retinopathy of prematurity (ROP).^{1–3} However, such therapy does not always prevent

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The authors have no relevant financial interest in this article.

progression of disease to retinal detachment. Case series have shown that scleral buckling and vitrectomy techniques can successfully reattach the retina of children with both stage 4 and stage 5 ROP.^{4,5} However, the visual results following such interventions have been disappointing.⁴⁻⁹ An exception has been the treatment of stage 4A with scleral buckling or lens-sparing vitrectomy, where better structural and visual outcomes have been reported in a number of case series.^{5,10-13}

The Early Treatment for Retinopathy of Prematurity (ETROP) Cooperative Group compared ablative therapy of high-risk prethreshold eyes with conventional management (ablative retinal surgery for “control” eyes upon reaching threshold, or observation of control eyes if threshold was not reached). The investigators found that early treatment of eyes with high-risk prethreshold ROP significantly improved the structural and functional outcomes.^{1,3} Some eyes progressed to retinal detachment. Treatment of retinal detachment was not part of the study protocol and therefore eyes with a retinal detachment were observed or treated, with both timing and procedure(s) (scleral buckling and/or vitrectomy) at investigator discretion. We have previously reported the structural and functional outcomes for those eyes at 9 months corrected age. In this report we provide follow-up through 6 years of age as well as the incidence of new retinal detachments in the ETROP cohort.

METHODS

Premature infants with birth weights less than 1251 grams who developed ROP were followed prospectively with standardized data collection in the ETROP study at 26 centers in 2000–2002. The study protocol was approved by investigational review boards of each participating nursery and written informed consent obtained from parents and guardians for all study procedures. Details of the protocol risk model have been previously published.^{1,14,15} Follow-up examinations continued to 6 years of age.

Eligibility for this report

Eligible children had at least one eye randomized in the ETROP Study. Eyes that are included had been randomized to either conventional management or early ablative treatment of high-risk prethreshold ROP and had at least one clock hour of retinal detachment seen in any zone prior to the 9-month corrected age examination. In addition the performance of vitreoretinal surgery prior to the 9-month corrected age study examination was considered evidence of retinal detachment, if a study form was not completed preoperatively (15 eyes). It is possible vitrectomy was performed in these eyes for other indications. A confirming examination of the retinal detachment was not required.

A second and separate group of subjects we have included in this report are those with no retinal detachment at 9 months, but were found to be detached at 6 years. There were 535 eyes which did not have a retinal detachment prior to 9 months and had 6-year follow up exams.³ The number and characteristics of eyes with a “late” detachment are described.

Procedures

Eyes that developed retinal detachment were not randomized. For eyes undergoing vitreoretinal surgery, the indications, timing and technique *were not* specified by the ETROP

study protocol, but were chosen and performed at the discretion of the investigator. For purposes of this report, vitreoretinal surgery includes vitrectomy, scleral buckling or both. Procedures were performed both by vitreoretinal surgeons located at ETROP Clinical Centers, as well as surgeons at non-participating facilities.

Study-certified ophthalmologists conducted retinal examinations at 6 years of age. The status of the retina was categorized 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), total retinal detachment (stage 5), and uncertain.¹⁶ Echography was utilized at the discretion of the examining physician.

Recognition letter optotype testing was performed at 6 years of age by traveling study certified testers masked to the child's treatment. ETDRS charts were used with a maximum distance of 3 meters (Precision Vision, LaSalle, Illinois) following a standardized protocol.³ Visual acuity testing was not performed on children unable to perform the test because of developmental limitations or if any of the following were present in both eyes: light perception or worse vision, retinal detachments, phthisis bulbi, or enucleation. Visual acuity results on the ETDRS testing were categorized as normal (20/40 or better), below normal (worse than 20/40 to better than 20/200), poor (measurable acuity of 20/200 or worse), or blind/low vision/light perception. Favorable acuity was defined by the ETROP study group as better than 20/200.

RESULTS

The study records of 401 randomized subjects were reviewed for the presence of a retinal detachment or the performance of vitreoretinal surgery (Figure 1). Retinal detachment and/or vitreoretinal surgery were reported in 89 eyes of 63 subjects.

Among the 13 infants (14 eyes) who did not undergo surgery, 3 died before the 6-year outcome exam, leaving 11 observation eyes from 10 subjects for analysis. Vitreoretinal surgery was performed in 75 eyes of 57 subjects. Among those that underwent surgery, 6 infants died (9 eyes) and 6 infants were not examined (7 eyes), leaving 59 eyes from 45 subjects evaluated at age 6 years. Thus, 70 of 89 eyes originally reported (79%) from 55 infants with retinal detachment were available for analysis. The 70 retinal detachments were classified as stage 4A in 28 eyes (40%), stage 4B in 14 eyes (20%), stage 5 in 13 eyes (19%), and not classified in 15 eyes (21%). Twenty-six of these 70 eyes (37%) had been randomized to early ablative treatment, while 44 (63%) had conventional management with laser ablation when they reached study threshold. The 49 surviving subjects who underwent surgery had a mean birth weight of 715 g and a mean post-menstrual age at birth of 25.1 weeks. The age at vitreoretinal surgery was not collected, although surgery was performed before 9 months corrected age.

Structural outcome

At 6 years of age attachment of the macula was noted in 25 of 70 eyes (36%). Two of 11 eyes (18%) had macular attachment following observation, 6 of 9 (67%) following scleral

buckle only, and 17 of 50 eyes (34%) following vitrectomy with or without scleral buckle (Table 1).

The eyes that underwent vitrectomy surgery were subdivided by ICROP classification of the retinal detachment at the time of the first vitreoretinal procedure (Table 1). Following surgery an attached macula was present in 5 of 16 eyes with stage 4A prior to surgery (31.3%), 6 of 10 with stage 4B prior to surgery (60%) and 0 of 10 with stage 5 prior to surgery.

The 50 eyes that underwent vitrectomy were subdivided by initial randomization with the structural outcomes listed in Table 2. Early treatment and conventional management had similar rates for partial or total reattachment.

Functional outcome

Favorable visual acuity was found in 6 eyes (1 normal and 5 below normal). (Table 3) Of those children with favorable acuities at age 6 years, 5 had been stage 4A and the sixth eye was not classified. Of those eyes with favorable visual acuity, 5 of 6 followed vitreoretinal surgery. Unfavorable acuity outcomes were classified into 4 categories: poor but measurable in 9 eyes, low vision card in 9 eyes, light perception in 7 eyes, and no light perception in 30 eyes. Vitreoretinal surgery for stage 5 ROP produced no eyes with better than light perception vision.

Structure and function after vitreoretinal surgery

The impact of the structural outcome on function is shown in Table 4 for the 59 eyes which had vitreoretinal surgery. Total retinal attachment was a reliable indicator for measurable visual acuity at 6 years. Of the 22 eyes in which the retinas were totally attached, 11 (50%) had measurable ETDRS visual acuity. Only 2 of the 8 with a portion of retina attached had measurable acuity, poor in both cases. Light perception was reported rarely by subjects with total detachments.

There were 11 eyes following vitreoretinal surgery with retinal attachment and measurable ETDRS visual acuity. (Table 4) The fellow eyes of these subjects were four eyes with stage 1, three eyes with stage 2, two eyes with stage 3, and one each with stages 4B and 5A.

“Late” detachment after 9 months

Of the 535 eyes that had no retinal detachment through the 9-month corrected age exam, only 2 eyes developed a detachment prior to age 6 years. The first subject had macular ectopia at 9 months, with a stage 4B detachment at 6 years and poor visual acuity by ETDRS. The second child had a normal exam at 9 months, with a stage 5B detachment (closed funnel) at 6 years and vision that could not be graded.

Discussion

Early retinal ablative treatment of high-risk prethreshold ROP reduced the rate of unfavorable structural and functional outcomes through 6 years of age.^{1,3} However, retinal detachment occurred in 89 of 718 randomized eyes (12%) before 9 months corrected age.¹

In the ETROP Study, infants with a retinal detachment were observed or underwent vitreoretinal surgery at the discretion of the individual investigator. There was no protocol for management of patients with a retinal detachment. Vitreoretinal surgery for retinal detachment in the ETROP study was associated with macular attachment in 17 of 56 eyes (30.4%) at 9 months corrected age. Visual acuity outcomes using forced-choice preferential looking at 9 months corrected-age were poor.⁵

This report describes the structural and functional outcomes of eyes with retinal detachment associated with ROP at age 6 years. Attachment of the macula was present in 25 of 70 eyes (36%) irrespective of treatment and in 23 of the 59 (39%) of the eyes that underwent vitreoretinal surgery and were available for analysis. With respect to visual acuity, 6 children had favorable ETDRS visual acuity at 6 years of age. Of these eyes, 5 of 6 had been stage 4A, while the other was not classified. No eye with stage 5 developed vision better than light perception. For stage 4B vision was restored in two eyes to poor. These results are worse than reported at 9 months corrected age, likely due to the more demanding optotype test used at age 6 years.

The 6-year visual function was compared with the final retinal structure. Total retinal reattachment was reported in 22 eyes. These eyes had a 23% chance of a favorable visual outcome as defined by the study group. Partial reattachment was rarely associated with measurable visual acuity and never with a favorable level. However, the cause for poor vision following successful reattachment is uncertain. Most of the fellow eyes of the subjects successfully undergoing vitreoretinal surgery with measurable visual acuity were less severely affected.

The ETROP study enrolled patients between 2000 and 2002, with vitreoretinal surgery taking place during that same period. These results are consistent with the findings of the CRYO-ROP Study which found poor visual outcomes with observation of a partial detachment in the late 1980's¹⁷ and no useful vision with either observation or vitreoretinal surgery for stage 5 disease.⁹

In the ETROP study vitrectomy for stage 4A was not as successful as reported in other case series.^{5,10-13} Outcomes in the ETROP may vary from such single-center series because of differing indications, timing of surgery, or experience of the vitreoretinal surgeons. For example, some authors have suggested that vitreoretinal surgery should be considered earlier in the disease course to achieve better attachment rates than were seen in CRYO-ROP or ETROP.^{10,11,13,18} Conversely, the ETROP Study results may represent more generalizable outcomes.

The strengths of the study include multicenter prospective design, standardized acuity testing, masked visual acuity testers, and 6 years of follow-up. There are important limitations to this report. First, the small number of eyes in each treatment category prevents comparison. Second, the classification of the retinal detachment in 15 eyes was not recorded prior to surgery. Third, there was no randomization of treatment of the retinal detachment. Fourth, there was no standardized approach for the indications, timing and techniques of vitreoretinal surgery. Surgeons recommended vitreoretinal surgery for differing levels of

severity of ROP and had varying experience. Fifth, the timing of surgical intervention was not standardized. In some cases timely vitreoretinal surgery may not have been done because of other medical issues for the infants.

We did observe late retinal detachments in children with a history of successful ablative therapy for high-risk ROP and attached retinas at 6 months corrected age.^{19–21} The rate of late retinal detachments was low with only 2 of 535 eyes affected by age 6 years. Our rate is much lower than that reported by Smith and Tasman, perhaps because they had longer follow up (average 35 years), their case series did not have complete cohort follow-up, and their patients had not been treated with retinal ablation.²¹ In spite of the low rate of late retinal detachment, we advocate periodic retinal examination of children with treated ROP because late detachments may be asymptomatic, as they may commence in the retinal periphery, or in a child with an attached retina in their fellow eye.

In conclusion, assessment of eyes with retinal detachment from ROP in the ETROP study at age 6 years found few children with favorable vision and then only following repair of stage 4A disease. Vitrectomy for stage 4A eyes was associated with macular attachment in 31% (5 of 16), with favorable vision noted in 6% (1 of 16). Vitrectomy for stage 5 produced one of 10 eyes with peripheral retinal reattachment and one of 10 eyes with light perception. These data confirm the difficulty of successfully reattaching the retina and obtaining useful vision once the retinal detachment has progressed to include the macula.

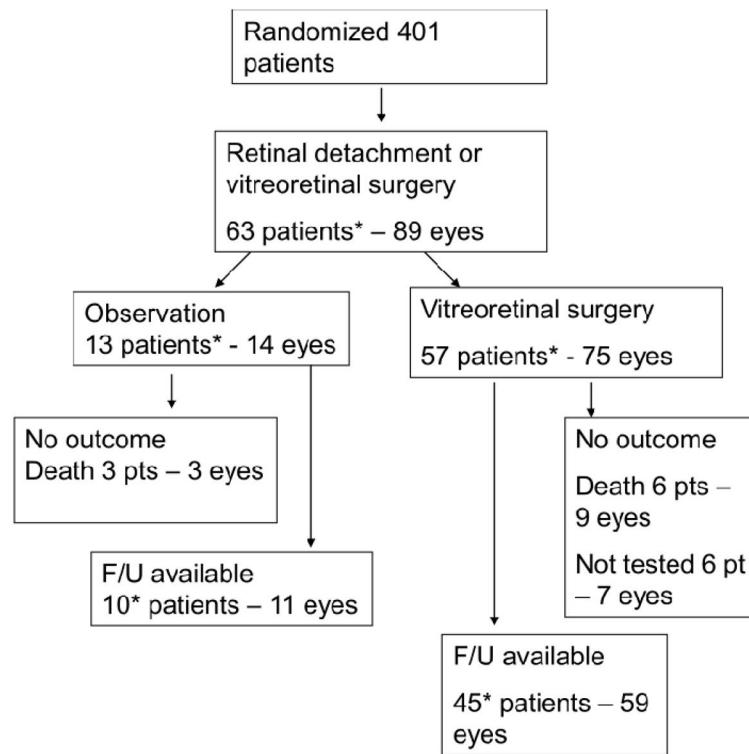
Acknowledgments

This study was supported by Cooperative Agreements 5U10 EY12471 and 5U10 EY12472 with the National Eye Institute, National Institutes of Health, Bethesda, Maryland.

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*6 patients had one eye in each group

Figure 1.

Flow Diagram for Subjects/Eyes with Retinal Detachment

Two patients developed a retinal detachment after 9 months corrected age and are not included in this figure.

Structural Outcome at 6 Years after Observation or Treatment for Retinal Detachment

Treatment by Preoperative ROP Stage at 6 Months	Structural Outcome at 6 Years						Total Eyes, No.
	Normal Posterior Pole	Totally Attached (Stage 4A)	Macula Attached (Stage 4A)	Some Retina Attached (Stage 4B)	(Stage 4C)	Total RD (Stage 5)	
Observation							
4A	2	1	...	2	1
4B	2	2
5	2	3
Scleral buckling							
4A	1	4	6
4B	2	2
Not classified or missing	1	1
Vitrectomy with or without scleral buckling							
4A	5	...	5	...	6	...	16
4B	1	4	1	1	2	1	10
5	1	2	...	10
Not classified or missing	1	5	...	1	7	...	14

Abbreviations: RD, retinal detachment; ROP, retinopathy of prematurity.
Ellipses indicate none.

[†] Indicates unable to grade because of inability to examine retina.

Stage 4C was defined by the study group to be a partial retinal detachment in which the macula cannot be seen because of cataract, corneal opacity, retrolental membrane or other obstruction.

Table 2

Structural Outcome at 6 Years for Vitrectomy Subgroup by ETROP Randomization: Early Treatment compared with Conventional Management

Treatment	Structural Outcome at 6 Years						Total Eyes, No.
	Normal Posterior Pole	Totally Attached	Macula Attached (Stage 4A)	Some Retina Attached (Stage 4B)	(Stage 4C)	Total RD (Stage 5)	
Conventional management	2	8	0	6	1	16	1
Early treatment	0	6	1	2	1	6	0

RD = retinal detachment

Ellipses indicate none.

[†] Unable to grade because of inability to examine retina.

Stage 4C was defined by the study group to be a partial retinal detachment in which the macula cannot be seen because of cataract, corneal opacity, retrolental membrane or other obstruction.

Table 3

ETDRS Visual Acuity Outcome at 6 Years for Children with Retinal Detachment after Observation or Treatment

Treatment by Preoperative ROP State at 6 Months	ETDRS Outcome at 6 Years						Total No. of Eyes	
	Favorable ETDRS			Unfavorable ETDRS				
	Normal	Below Normal	Poor	Low Vision Card Only	Light Perception Only	No Light Perception		
Observation								
4A	1	...	1	2	1	...	1	
4B	2	...	
5	1	1	1	
Scleral buckling								
4A	...	3	1	1	1	
4B	1	1	
Not classified or missing	1	1	
Vitrectomy with or without scleral buckling								
4A	...	1	2	4	1	7	16	
4B	2	1	1	3	10	
5	1	8	10	
Not classified or missing	...	1	3	1	2	7	14	

ETDRS visual acuity categories: normal (20/40 or better), below normal (worse than 20/40 to better than 20/200), poor (measurable but worse than 20/200)

Abbreviation: ROP, retinopathy of prematurity.

Ellipses indicate none.

Correlation of Structure and Function for Eyes Undergoing Vitreoretinal Surgery

ETDRS Outcome at 6 Years	Structural Outcome at 6 Years						Total Eyes, No. (%)
	Totally Attached	Macula Attached (Stage 4A)	Some Retina Attached (Stage 4B)	(Stage 4C)	Total RD (Stage 5)	Unable to Grade	
Favorable ETDRS acuity	5	5(8)
Poor but measurable ETDRS acuity	6	...	2	8(14)
Low vision card only	3	...	3	...	1	...	7(12)
Light perception only	1	...	4	...	5(8)
No light perception	6	...	1	2	17	1	27(46)
Unable to perform	2	1	1	...	2	1	7(12)

ETDRS visual acuity categories: normal (20/40 or better), below normal (worse than 20/40 to better than 20/200), poor (measurable but worse than 20/200)

Abbreviation: RD = retinal detachment.

Ellipses indicate none.

Stage 4C was defined by the study to be a partial retinal detachment in which the macula cannot be seen because of cataract, corneal opacity, retroental membrane or other obstruction.