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Surgical Management of Retinopathy of Prematurity

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Abstract

Purpose of review—The surgical management of ROP continues to employ a paradigm of peripheral laser followed by vitrectomy for patients who develop retinal detachment. This review addresses significant advances that have been made in our understanding of the indications, timing, techniques, and outcomes of these interventions.

Recent findings—The indications for laser are highly dependent upon the diagnosis of plus disease. Recognition of plus disease is variable and subjective. Efforts are underway to develop more objective measures of plus using image analysis software. Intravitreal injection of bevacizumab is emerging as an adjunct to laser for aggressive posterior ROP. While vitrectomy for retinal detachment is effective in eyes without plus, management of eyes with retinal detachment and persistent plus continues to be a major challenge. Older children with regressed ROP may suffer from vitreous hemorrhage in the absence of retinal tears, detachments, or active neovascularization.

Summary—Our understanding of the best indications, timing and techniques for the surgical management of ROP continues to evolve and outcomes have improved in recent years. Areas that generate significant ongoing interest and investigation include the assessment of plus disease and the use of adjuncts for aggressive posterior ROP.

Keywords

retinopathy of prematurity; plus disease; laser; retinal detachment; vitrectomy

Introduction

While there have been exciting new advances in our understanding of the surgical treatment of ROP, the basic tools available to the ophthalmologist have not changed dramatically in recent years. The initial vasoproliferative manifestations of the disease are managed with ablation of the peripheral retina and the subsequent cicatricial manifestations are treated with incisional surgery designed to relieve traction. This paradigm has been in place since the 1980s. Important insights have been gained, however, into the indications, timing, and techniques for performing these basic functions. In addition, our understanding of complications and outcomes of ROP treatment has improved significantly. This review will consider the most recent literature regarding laser ablation and incisional surgery for the acute phase of ROP as well as important articles about delayed vitreoretinal manifestations of the disease.

Acute Phase: Laser Ablation

This section discusses the indications, technique, outcomes and complications of laser for ROP. In addition, emerging reports on the use of bevacizumab as an adjunct to laser are reviewed.

Indications for Laser

The indications for ablative treatment of the avascular retina for acute phase ROP were initially established by the results of the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) published in 1988.¹ Recommendations from this study were for treatment at a threshold of severity defined as stage 3 disease involving 5 contiguous clock hours or 8 cumulative clock hours in zone I or II. These recommendations were the standard of care for over 15 years until the findings of the Early Treatment for Retinopathy of Prematurity Trial (ETROP) resulted in revision of the indications for treatment in 2003.² The ETROP compared outcomes of early treatment with outcomes of treatment performed according to the guidelines established in the CRYO-ROP study. Early treatment was performed in randomly selected eyes with high risk prethreshold ROP. Results of the study showed a significant reduction in unfavorable structural outcomes at 9 months from 15.6% in eyes managed according to CRYO-ROP guidelines to 9.1% for eyes managed with early treatment ($p<.001$). Analysis of the data, however, revealed that a substantial number of eyes with high risk prethreshold disease were treated when, with observation, similar eyes did well in the conventionally managed group. Based on this post hoc analysis, it was determined that eyes with high risk prethreshold ROP, but without plus disease, could safely be observed until they developed plus disease. A clinical algorithm was established that would have resulted in fewer eyes treated while maintaining the advantage of early treatment for eyes at highest risk for adverse outcome. The clinical algorithm used plus disease as the most important feature for decision making. This algorithm divided prethreshold ROP into types 1 and 2 and recommended that treatment be considered for type 1. Type 1 was defined as follows:

Zone I, any stage ROP with plus disease

Zone I, stage 3 ROP with or without plus disease

Zone II, stage 2 or 3 ROP with plus disease

All other high risk prethreshold ROP was considered type 2 ROP. For type 2 ROP the study recommended continued observation with close follow-up. Plus disease was defined in the study as dilation and tortuosity of the posterior retinal blood vessels in at least 2 quadrants, meeting or exceeding that of a standard photograph. The standard photograph of plus disease was the same as that used for the CRYO-ROP study in the 1980s.

Although the findings of the ETROP define the indications for laser used in clinical practice today, current controversy over ETROP recommendations exists in two areas. First, despite the treatment algorithm designed to minimize unnecessary treatment, concerns persist about treating eyes that otherwise would have undergone spontaneous regression without treatment.³ Second, the subjective nature of assessing plus disease, and the importance of that assessment in treatment decisions, continue to generate significant interest and clinical investigation.⁴⁻⁶ And even as significant attention in the literature has been paid to potential pitfalls in recognizing plus disease, the International Committee for the Classification of ROP has recently defined pre-plus disease.⁷ Pre-plus disease consists of abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilation than normal. Thus, there are now 3 categories for the appearance of vessels in the posterior pole of eyes with ROP: plus, pre-plus, or neither.

A recent article by Wallace et al compared assessment of plus and pre-plus among 3 experienced ROP examiners who evaluated 181 high-quality RetCam images from premature infants.⁶ The study found that there was disagreement on the presence of plus disease for 10% of the images and, among images with pre-plus or worse, there was disagreement 27% of the time. In a similar study by Chiang et al⁵, images were evaluated by 22 ROP experts and agreement on the presence or absence of plus disease by all examiners was found in only 7 of 34 images (21%).⁵ Using a 3 level categorization (plus, pre-plus, or neither), they found agreement among all 22 experts in only 4 of 34 images (12%). These studies conclude that the large amount of inter-observer variability indicates that even experts in ROP frequently disagree on the diagnosis of plus disease.

Efforts to quantify more consistently and accurately retinal vascular dilation and tortuosity have resulted in several important publications. A study by Johnson et al evaluated fundus photos captured by the NM200D fundus camera (Nidek, Inc, Aichi, Japan).⁸ Retinal vascular diameter was measured using VesselMap semi-automated software. Vessels in eyes with plus disease were compared to vessels without plus disease in controls matched for birth weight and gestational age. The mean venous diameter was significantly larger in the plus disease group ($p=0.39$). Another paper by Wallace et al reported on the use of a computer program (ROPtool) to measure tortuosity.⁹ The computer accuracy for detecting tortuosity sufficient of plus disease was 95% (175 of 185 images), and compared favorably to 3 pediatric ophthalmologists who also evaluated the images. These studies, along with others, suggest that computerized analysis of digital images may offer an objective way to diagnose plus disease.¹⁰⁻¹³ In addition, these studies suggest that plus disease may be diagnosed remotely with telemedicine strategies.

Alternative metrics of retinopathy, and of prematurity will, over time, most likely become increasingly sophisticated and may in the future allow for completely new more objective treatment criteria. A study by Rabinowitz et al showed that severe ROP can be predicted weeks ahead of the traditional manifestation of severe disease by measuring retinal vascular diameter at 31 to 34 weeks post conceptual age.¹⁴ In another study, infant growth rates and serum IGF levels were found to be predictive of which neonates would progress to severe ROP needing treatment.¹⁵

Laser Technique

Laser photocoagulation with confluent or near confluent application of burns using indirect ophthalmoscopic delivery has gained wide acceptance and is the preferred technique for ablation of the avascular retina in ROP. Indirect ophthalmoscopic laser is generally considered to be technically easier to perform than cryotherapy and multiple articles have shown laser to be at least equivalent to cryotherapy in terms of outcome.¹⁶⁻²⁰ In addition, laser is preferable to cryotherapy because laser is associated with less inflammation and reduced stress on the neonate.²¹

Further refinements of the laser procedure to minimize stress and expense by performing the procedure without endotracheal intubation have been reported. Recent work has shown that sedation without endotracheal intubation works well in many cases and may reduce ventilator dependence along with associated ventilator complications and costs.²²⁻²⁴ Our own experience has been consistent with the published literature that laser for ROP can be performed without intubation in most cases.

Adjuncts to Laser Surgery

Laser ablation of the avascular retina causes regression of ROP because it destroys a pathologic source of vascular endothelial growth factor (VEGF). The role of VEGF in the

pathogenesis of ROP is firmly established and this subject has been well reviewed elsewhere.²⁵ Bevacizumab (Avastin) is a monoclonal antibody fragment that binds all isoforms of VEGF A. It has been approved by the FDA to treat metastatic colon cancer and it has also been used effectively, as an intravitreal injection, in adult neovascular eye diseases including age-related macular degeneration²⁶ and diabetic retinopathy.²⁷ Recently several articles have reported cases of ROP treated with intravitreal bevacizumab.²⁸⁻³¹ Results have generally been good in these isolated case reports and small case series. Most recently, however, there has been a report of adverse contraction of proliferative membranes after bevacizumab injection. In this patient, one eye was treated with intravitreal bevacizumab after failed laser for zone I ROP. After the injection, the vascular activity resolved but acute membrane contraction resulted in a funnel-shaped retinal detachment.³² As an explanation of the findings, the authors credit bevacizumab for causing not only rapid regression of neovascularization but also accelerated fibrosis and contraction of the posterior hyaloid.

Currently underway in the United States is a multicenter prospective phase I safety trial of intravitreal bevacizumab for zone I ROP that fails laser. Infants with bilateral zone I ROP and persistent plus disease after laser will have one eye randomly assigned to receive 0.75 mg of intravitreal bevacizumab. A centralized reading center will evaluate serial RetCam images from each eye weekly after the injection and these images will be compared to the contralateral control eye. A total of 22 infants are to be enrolled from 11 clinical centers. A larger efficacy study is planned if safety is demonstrated in the phase I trial.

Laser Outcomes and Complications

Ablative treatment in the ETROP study resulted in a reduction of unfavorable visual acuity outcomes from 19.5% to 14.5% and reduction of unfavorable structural outcomes from 15.6% to 9.1% at 9 months.² Early treatment was associated with more apnea and bradycardia, and a higher rate of reintubation for mechanical ventilation compared to standard treatment in the ETROP. There was no difference however between the groups for ocular complications, mortality, or known permanent morbidity.

The 2 year structural outcomes of the ETROP were recently published and structural outcomes found at 9 months were stable at 2 years (9.1% unfavorable).³³ Visual results will be studied when the cohort is 6 years old. At 1 year the corresponding rate of unfavorable structural outcomes for the CRYO-ROP was 25.7% and at 3 1/2 years it was 26.1%.^{34, 35} Interestingly, the 2 year unfavorable rate in the ETROP for the cohort managed according to the conventional CRYO-ROP indications was 15.4%. Why the improvement in outcomes between these 2 studies even for the cohorts that were managed according to the same guidelines? The superiority of laser over cryotherapy is one potential explanation. Another is that examiners for the ETROP were “calibrated” differently than those for the CRYO-ROP such that the severity of ROP for any given eye was graded towards earlier treatment even in the cohort managed by the older CRYO-ROP guidelines. The difference in outcome is more striking when considering that patients randomized in the ETROP were pre-selected as being high risk, were more likely to have ROP in zone I, and on average had lower birth weight than patients in CRYO-ROP.

Whether early treatment as performed in the ETROP will increase or decrease the risk of later complications is currently unknown. The CRYO-ROP found that there continued to be a significant number of patients progressing to unfavorable outcome even out to 15 years after treatment.³⁶ Whether earlier treatment with more posterior disease and more extensive ablation will lead to increased late complications is unknown. The stability of the ETROP structural findings at 2 years is, at least, hopeful in this regard.

Acute Phase: Treatment of Retinal Detachment

This section discusses the use of surgical techniques to manage tractional manifestations of ROP.

Vitrectomy and Scleral Buckle

Despite timely and thorough laser as performed in the ETROP study, almost 1 in 10 infants treated with laser for ROP will develop unfavorable structural outcomes. Results of surgery on eyes with stage 4 retinal detachment in the ETROP were generally disappointing with only 67% (6 of 9) reattached with scleral buckle and only 33% (15 of 45) reattached with vitrectomy.³⁷ These results contrast with results of other published studies of vitrectomy for stage 4 ROP where reattachment rates have been in the range of 80 to 90%.³⁸⁻⁴² One possible explanation for the difference is that eyes in the ETROP that developed retinal detachment may have been eyes with more vascular activity and generally more severe ROP. The other studies on vitrectomy for stage 4 ROP included eyes that were managed in the pre-ETROP era and likely included eyes that detached due to delayed treatment of ROP that was inherently less severe. Such eyes, had they been managed as part of a clinical trial according to rigorous protocols, likely would not have detached in the first place. The ETROP eyes that detached, in other words, may have had inherently more severe disease with neovascular activity and plus more refractory to laser treatment and thus more likely to progress and fail despite any intervention.

The operative technique most commonly utilized for tractional stage 4 ROP is 2-port, lens-sparing vitrectomy (LSV) although good results have been reported with 3-port LSV as well. Vitrectomy is generally considered superior to scleral buckling (SB) alone for stage 4 ROP⁴³ but until recently there were no comparisons in the literature between LSV and LSV combined with SB. A recent study by Sears et al found that the addition of scleral buckling to vitrectomy did not improve outcomes.⁴⁴

The key to successful outcome is to operate after the neovascular activity and plus disease have completely or almost completely resolved. Performing vitrectomy before resolution of this vascular activity may be associated with bleeding, increased exudation, or with continued proliferation and contraction after the vitrectomy. In some instances however, detachment may progress rapidly after laser ablation before the plus disease and neovascular activity have a chance to resolve. This is more likely to be the case for more posterior ROP. Since the adoption of ETROP treatment guidelines, we have seen fewer stage 4A retinal detachments. In general, the eyes that fail despite early treatment are those that are inherently more severe and more likely to progress to total detachment before the neovascular activity and plus resolve. Effective surgical management of these eyes represents a major ongoing challenge.

Aggressive Posterior ROP (APROP)

APROP is a form of ROP that has not been recognized as a distinct entity until fairly recently. Previously this form of ROP had been known as “rush disease” but had not been included as a specific category in the International Classification of ROP. The International Committee for the Classification of ROP recently issued revisions that defined APROP and this entity deserves mention here as it has been the subject of several articles on surgical management.⁷ APROP is defined as an uncommon, rapidly progressing, severe form of ROP. The characteristic features are its posterior location (usually zone I but also posterior zone II), prominent plus disease in all 4 quadrants out of proportion to the more peripheral findings, and a deceptively featureless junction between vascularized and avascular retina. It may display flat neovascularization and does not usually progress through the classic ROP

stages 1 to 3. APROP has a particularly poor prognosis with laser alone and a high percentage progress to retinal detachment despite laser.

Data from the Photographic Screening for Retinopathy of Prematurity (PHOTO-ROP) Study included 5 patients with bilateral APROP treated with near confluent laser ablation. Progression to retinal detachment was documented photographically in these study patients and the findings of an analysis of these photos were recently published.⁴⁵ Findings included the observation that flat neovascularization may obscure avascular retina and that this tissue contracts after laser revealing large untreated areas. In addition, plus disease was found to regress initially after laser only to recur later with progression to retinal detachment.

Several recent articles describe treatment of APROP using laser combined with vitrectomy. A study from Italy reviewed cases of APROP in 13 eyes treated with LSV after laser but before retinal detachment appeared.⁴⁶ All eyes had attached retinas at mean follow-up of 13.5 months. An earlier study from Japan examined outcomes of APROP treated with LSV or vitrectomy with lensectomy.⁴⁷ The vitrectomies in this series were performed after partial detachment of the retina but before resolution of neovascular activity and plus. Six eyes had LSV and all had poor outcome with progressive traction. By contrast, the 16 eyes in the series that underwent vitrectomy with primary lensectomy all had complete retinal reattachment with one operation.

Formalized guidelines for managing APROP do not exist at present and treatment modalities are in a state of evolution for this rare form of ROP. Future directions of treatment may be influenced by a theory that the pathogenesis of APROP is distinct from that of classic zone II ROP.⁴⁸ This theory holds that APROP results from perturbations in early retinal *vasculogenesis* as opposed to the abnormalities in later *angiogenesis* that result in zone II ROP. Time will tell if this theory leads to new interventions for APROP.

Adjuncts to Vitrectomy for Stage 5 ROP

Historically the results of surgery for stage 5 ROP have been poor both anatomically and visually. One recent review of a large cohort operated by a single surgeon over many years found an anatomic success rate of 28% and this is similar to other published series.⁴⁹ Improved results have been reported in 2 articles describing vitrectomy performed in combination with pharmacologic adjuncts. The first of these described the use of intravitreal triamcinolone (2.0 mg/0.05 ml) injected at the end of the vitrectomy procedure in 10 eyes with vascularly active stage 5 ROP.⁵⁰ All eyes had prior zone I disease and at the time of surgery had persistent vascular engorgement and neovascular activity. The anatomic success rate in this very difficult patient population was 60%. A similar group of 11 eyes undergoing vitrectomy without adjunctive triamcinolone had anatomic success in no cases. The investigators concluded that success in the triamcinolone group was due to the drug's ability to cause resolution of plus disease and involution of neovascularization.

A second article on the use of an adjunct to vitrectomy described the use of autologous plasmin for stage 5 ROP.⁵¹ These authors reported complete reattachment of the posterior pole in 6 out of 6 consecutively treated eyes with stage 5 ROP. They compared these results to earlier work in which the same surgeon achieved anatomic success in 47% of stage 5 cases without plasmin. Plasmin is known to cleave laminin and fibronectin and can assist in separating cortical vitreous from the surface of the retina. Its successful use has been reported previously for both adult⁵² and pediatric vitrectomy.⁵³ The authors concluded that plasmin facilitated successful repair in these stage 5 ROP eyes by weakening adhesions between proliferative membranes and the retina.

Delayed Vitreoretinal Manifestations of ROP

Patients with regressed ROP continue to be at risk for vitreoretinal diseases for a lifetime. The mechanism underlying late posterior segment disease is the persistence of abnormal vitreoretinal traction. Manifestations of abnormal vitreoretinal traction in eyes with regressed ROP have been well described. These tractional forces are known to cause avulsion of retinal vessels⁵⁴, retinal tears⁵⁵, and retinal detachments in children⁵⁶⁻⁵⁸ and adults⁵⁹⁻⁶¹ with regressed ROP. Recently vitreous hemorrhage has also been identified as a sequela of abnormal vitreoretinal traction in older children with regressed ROP.⁶² In our review of all children with vitreous hemorrhage at our institution, regressed ROP was found to be the most common causes of spontaneous hemorrhage.⁶³ In contrast to work by Huthcheson et al⁶⁴ that found vitreous hemorrhage in acute, high-risk ROP to be a poor prognostic sign, we found that the majority of patients with regressed ROP and late vitreous hemorrhage maintained baseline vision. Most patients in our series had no evidence of a retinal tear or retinal detachment, and none had active neovascularization. Our experience has been that many eyes with regressed ROP and vitreous hemorrhage, particularly in children old enough to no longer be at risk for amblyopia, can safely be observed and that many will clear spontaneously.

Conclusion

In conclusion, the current surgical management of ROP continues to employ laser ablation followed by vitrectomy if retinal detachment develops. Our understanding of the best indications, timing, and techniques for performing these interventions has improved significantly, as has our understanding of outcomes. Investigation continues into more objective ways to measure plus. Adjunctive use of bevacizumab is emerging as an adjunct for APROP. Stage 4 ROP in eyes with regressed plus show good anatomic outcomes with vitrectomy. The management of eyes with persistent neovascular activity after laser and of stage 5 ROP continues to represent a major challenge.

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