Laser Treatment for Retinopathy of Prematurity

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Abstract

Retinopathy of prematurity (ROP) has been established as the primary cause of visual impairment in premature infants. While cryotherapy used to be a method to treat this condition, laser photocoagulation with indirect ophthalmoscopic delivery has become the gold standard for threshold ROP treatment. This chapter discusses various defining criteria for stages of ROP, conclusions from significant studies such as the ETROP trial, as well as techniques for performing laser photocoagulation and achieving minimal complications. Addressing skip areas using wide-angle photography is a crucial step in ensuring angiogenesis. The next steps, including the role of anti-VEGF (vascular endothelial growth factor) agents in ROP as evident in the BEAT-ROP and RAINBOW trial is promising but requires further results.

Keywords

Retinopathy of prematurity · Skip areas · Angiogenesis Laser photocoagulation · Threshold ROP · Pre-threshold ROP · Diode laser · Anti-VEGF · Cryotherapy · Laser pattern

Retinopathy of prematurity (ROP) has been established as the primary cause of visual impairment in premature infants [1]. With increased survival of extremely low birth weight infants in recent years, it has been reported to be present in more than 84% of survivors born at <28 weeks of gestation [1]. Unlike the normal central to peripheral development of retinal vascularization, phase 1 of the pathogenesis of ROP involves initial vasoconstriction, arrested vessel growth, and relative hyperoxia, followed by phase 2 of relative hypoxia and abnormal vascular proliferation [2]. Supplemental oxygen to improve pulmonary function in premature infants after birth causes postnatal hyperoxemia, which leads to cessation of retinal vasculature maturation and development of a ridge that delineates peripheral avascular and central vascular retinal tissue [1]. The resulting retinal hypoxia induces the release of vascular endothelial growth factors and rapid angiogenesis and the occurrence of ROP [3]. ROP is zoned and staged based on the appearance of vessel at the interface of the vascular and avascular retina [4] Treatment for ROP is most effective during a small time period, making early recognition of disease crucial.

11.1 Cryotherapy

The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) was one of the first organized attempts to establish the role and efficacy of a therapeutic intervention for ROP. Threshold ROP was defined as at least five contiguous or eight total clock hours of stage 3 disease in zone 1 or 2, or the presence of plus disease [5]. There was an overall 49.3% reduction at 3 months and a 45.8% reduction at 12 months in the rate of unfavorable outcomes in cryotherapy treated versus non-treated eyes (Table 11.1) [5, 6]. With long-term follow-up, the reduction in risk of unfavorable structural outcomes was 43.2% at 10 years and 30% at 15 years [12, 13]. In terms of visual acuity and function, at the 10-year follow-up, 25.2% of treated eyes achieved visual acuity of 20/40 or better, compared to 23.7% of controls [12]. At 15-year follow-up, 44.7% of treated eyes and 64.3% of control eyes had developed unfavorable visual acuity outcomes, emphasizing the need for follow-up of patients with threshold ROP disease on a long-term basis [13].

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11.2 Laser Photocoagulation

While cryotherapy was extremely efficacious in treating ROP, it proved to be limited in its ability to target posterior areas within the eye. Given its ability to provide targeted treatment without invasive measures to the external eye and need of general anesthesia, laser photocoagulation presented as a more convenient option. The establishment of the laser photocoagulation with indirect ophthalmoscopic delivery as the standard treatment for threshold ROP replaced the role of cryotherapy. Preliminary studies after the introduction of laser photocoagulation as a treatment option for threshold ROP suggested that laser therapy was safe and at least as effective as cryotherapy in treating stage 3+ ROP (Table 11.1) [7, 8, 14, 15]. Comparison of the efficacy of laser photocoagulation and cryotherapy at 7-year and 10-year follow-up showed laser-treated eyes to have a superior mean best-corrected visual acuity (BCVA) of 20/33 and 20/66 compared with 20/133 and 20/182 in cryotherapy-treated eyes, respectively [16, 17]. Eyes treated with cryotherapy were 7.2 times more likely to develop retinal dragging compared with laser treatment [17]. This may have been secondary to the superior ability of the laser to treat more avascular retina in infants with posterior disease, where it is difficult to treat with cryotherapy. Looking at refractive outcome, laser-treated eyes were less myopic with a mean spherical equivalent (SE) of −4.48 D than cryotherapy-treated eyes (mean SE of −7.65 D) [18].

Table 11.1 Summary results for key studies evaluating the success of laser treatment for retinopathy of prematurity

Study name	Year published	Success rate of therapeutic intervention[a]
CRYO-ROP[b]	1990 [6]	78.2% with favorable outcome at 3 months
Argon laser for Stage 3+ ROP[c]	1991 [7]	93.8% (n = 15 of 16) at 3 months
Diode laser for Stage 3+ ROP[d]	1992 [8]	89.3% (n = 25 of 28) at 3 months
ETROP[e]	2004 [9]	85.7% with favorable outcome at 9 months
BEAT-ROP[f]	2011 [10]	74.0% (n = 54 of 73) at 54 weeks
RAINBOW[g]	2008 [11]	66.2% (n = 45 of 68) at 24 weeks

[a]The therapeutic intervention being studied is laser photocoagulation in all studies except CRYO-ROP, which evaluates cryotherapy vs. observation in infants with threshold ROP
[b]The CRYO-ROP study evaluated initial anatomic success of cryotherapy vs. observation at incremental periods of follow-up
[c]This study evaluated the efficacy of argon laser vs. cryotherapy
[d]This study evaluated the efficacy of diode laser vs. cryotherapy
[e]Primary outcome in ETROP was related to visual function. Also, while providers in ETROP had the option to use cryotherapy or laser photocoagulation on patients, all but one patient received laser treatment
[f]The BEAT-ROP studied the rate of recurrence at 54 weeks postmenstrual age as the primary outcome. The above results are for the combined pool of Zone I and Zone II posterior ROP. For Zone I only eyes, the results were 58.0% success (n = 19 of 33 eyes)
[g]The RAINBOW study evaluated the efficacy of two different doses of ranibizumab (0.1 and 0.2 mg) versus laser photocoagulation at maintaining absence of active ROP or absence of unfavorable structural outcomes

Given that a large percentage of infants with ROP continued to face poor visual and structural outcomes despite the developments in treatment, the Early Treatment of ROP (ETROP) trial was conducted to define the role of earlier treatment in infants at high risk of developing threshold ROP or unfavorable structural or visual acuity outcomes. Infants with pre-threshold ROP or considered high risk based on RM-ROP2 analysis were randomized to early peripheral retinal ablation or conventional management of monitoring for progression to threshold ROP [19]. Pre-threshold ROP was defined as any ROP less than threshold in zone I; zone II stage 2 with plus disease; zone II stage 3 without plus disease; or stage 3 with plus disease less than threshold criteria. Unfavorable structural outcomes were reduced from 15.6% to 9.0% ($p < 0.001$) at 9 months, and unfavorable visual acuity outcomes decreased from 19.8% to 14.3% ($p < 0.001$). Based on the findings, type I ROP, defined as zone I, any stage ROP with plus disease; zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 with plus disease, were at high risk of developing threshold disease and thus, retinal ablative therapy was recommended. On the other hand, type II ROP, defined as zone I, stage 1 and 2 without plus disease; or zone II, stage 3 without plus disease, could be monitored for progression [9]. The overall anatomic success of laser at 9 months in ETROP was 84.4% (Table 11.1).

A comparison of application with argon green (514 nm) and diode red (810 nm) laser suggested a preference for diode laser given the lower risk of burns to the tunica vasculosa lentis and cataracts with the latter due to deeper retinal lesions. It is important to acknowledge that ablative therapy is associated with acute complications and risks of corneal edema, intraocular hemorrhage, and cataract formation [20]. Initial laser settings often involve a power of 200–300 mW for 0.1–0.2 s, with a targeted burn of whitish-gray color. The laser power is then altered based on the area of treatment; less energy is used for the anterior and superior retina in comparison to the posterior and inferior retina, as well as retinal tissue close to the ridge. Typically, the procedure begins with a demarcation involving one row of laser with ¼ to ½ spot width separations anterior to the ridge and one row posterior to the ora serrata filling in all locations. The nasal and temporal areas over the ciliary artery and nerve utilize 1 to 1½ spot width separations in order to avoid undue damage to these structures. It is essential to treat the entire avascular retina, extending from the ridge (but not including the ridge) to the ora serrata [21]. Performing careful binocular indirect ophthalmoscopy often coupled with wide-angle photography following treatment is helpful to objectively determine if

skip areas are present [22]. Any skip areas should be immediately treated and the process of objective photography repeated until no skip areas remain.

As laser photocoagulation became accepted as the standard treatment for threshold ROP, studies focused on optimizing the technique of laser treatment to control disease progression. Banach et al. evaluated the role of the density of laser patterns in the progression of threshold ROP. Compared to the commonly utilized density of 1 to 1.5 burn widths apart, the study found that patients with a near confluent pattern laser treatment (spaced approximately 0.25 burn width apart) had a significantly lower rate of progression of disease to stage 4 or 5 (3.6% overall near confluent vs. 29% overall fixed density, $p = 0.0003$) [23]. Therapeutic ablation of the ischemic avascular retina observed in threshold ROP suppresses the angiogenesis stimulated by vascular endothelial growth factor, which may help with the resolution of ROP. Additionally, the therapy may also promote chorioretinal adhesions, resulting in positive outcomes; however, given that a proportion of eyes with zone 2 disease still progress to retinal detachments [23], this may be a smaller component [24]. A nearly confluent pattern of laser photocoagulation was also found to reduce the rate of re-treatment of the disease (0% of patients with zone 2 disease) [25].

Following laser treatment, it is imperative that a complete viewing of the retina be performed to ensure that no "skip" areas are identified (see Chap. 12, Fig. 4). "Skip" areas may prevent the regression of active vessels and disinhibit the growth of new vasculature, resulting in possible treatment failure. In a retrospective manner, Kang et al. evaluated the most common locations of skip areas as well as the role of using wide-angle digital imaging in training for the treatment of retinopathy of prematurity. The majority of skip areas occurred in the superior and inferior retina, likely due to a more difficult visualization of these regions and differences in the skill level of trainees that participated in the study. Skip areas missed during the initial treatment procedure were easily visualized with wide-angle digital imaging, making it a very helpful tool for ablative treatment related to ROP [22].

The course of ROP subsequent to treatment is of significant importance as complications including retinal detachments leading to subsequent blindness can occur. Coats studied involution patterns of ROP subsequent to laser photocoagulation in detail and the risk of downstream complications in 262 eyes of 132 infants. Complete ROP involution was noted in 80% of eyes within the first 28 days of treatment. Eyes with "clinically important" vitreous organization (defined as two or more dense, contiguous clock hours that significantly reduced visualization of the underlying retina) and vitreous hemorrhage (completely obscuration of retina visualization) were associated with statistically significant increases in the odds of a retinal detachment, making them strong predictive markers. Based on these results, a possible role for preemptive, instead of deferred vitrectomy, in some eyes with clinically important vitreous organization and hemorrhage was suggested [26]. Hartnett and McColm focused their analysis on understanding features that indicated eyes at risk of developing progressive stage 4 ROP requiring surgical intervention after laser treatment for threshold ROP. Absence of clear vitreous, six or more clock hours of ridge elevation, and plus disease in two or more quadrants were all found to be predictive of stage 4 ROP, while neovascularization was not prognostic according to this study. While unclear, the breakdown of the blood–retinal barrier and thickening of the vascular ridge secondary to growth factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor may be responsible for the increased vitreous haze and ridge elevation [27].

11.3 Ongoing Treatments

Numerous novel therapeutics are currently under investigation as the pathophysiologic mechanisms behind the occurrence of retinopathy of prematurity become better understood. Given that the ROP is known to develop in two phases of vaso-obliteration followed by neovascularization, ischemia is a major contributor to the disease, recruiting VEGF as a key factor in the process of angiogenesis. As with other diseases involving neovascularization, anti-VEGF therapies may have a promising role in the treatment of ROP. Current anti-VEGF agents such as bevacizumab, ranibizumab, and pegaptanib sodium have all been reported as treatment options in relation to ROP [28–31].

The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) trial was the first attempt at prospectively study the role of bevacizumab (0.625 mg per 0.025 ml) as primary therapy for ROP, in lieu of laser photocoagulation. The prospective, randomized, unmasked, stratified, multicenter Phase II trial assessed the role of intravitreal bevacizumab as primary therapy for zone I or II posterior stage 3+ ROP. For zone I, stage 3+ disease, the rate of recurrent retinal neovascularization within 54 weeks of treatment to was significantly higher in the group that received laser therapy in comparison to the group that received bevacizumab (42% vs. 6%; 95% CI (0.02 to 0.43), $p = 0.002$). Difference was noted for posterior zone II disease between the two groups, albeit not statistically significant ($p = 0.27$). The time to recurrence for zone I eyes was significantly different between the two groups 19.2 ± 8.6 weeks vs. 6.4 ± 6.7 weeks for bevacizumab and laser, respectively. Overall, laser success was suboptimal at 74.0% in the BEAT-ROP trial (Table 11.1). Based on these results, the authors concluded that bevacizumab was superior to laser for the treatment of zone I, stage 3+ ROP [10]. However, further

correspondence subsequent to this study has questioned the safety of bevacizumab in treating ROP, as well as the time of follow-up necessary to account for later recurrence in some infants subsequent to bevacizumab therapy [32–41].

The RAINBOW Phase III study (RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity), which is also randomized, open-label, controlled, and multicenter, is being conducted to assess the efficacy and safety of ranibizumab (0.1 and 0.2 mg) in comparison to laser photocoagulation in patients with ROP. Preliminary results indicate the percentage of infants with the absence of active ROP or unfavorable structural outcomes at 24 weeks to be 80% in the ranibizumab 0.2 mg, 75% in the ranibizumab 0.1 mg, and 66.2% in the laser-treated group (p = 0.0254; CI: 0.99 to 4.82) (Table 11.1) [11]. However, further information and analysis of the results is necessary before any conclusions can be made about possible changes in practice.

While anti-VEGF agents show a promising role in future treatment options of ROP—either as primary or adjuvant treatment—a tremendous amount of investigation needs to occur in order to better understand its long-term safety, efficacy, and treatment protocols prior to its acceptance as a mainstay therapy. Along with VEGF inhibitors, therapeutics targeting other mediators involved in the development and progression of ROP, such as EPO and IGF-1 are also under investigation and may offer promising avenues of treatment for ROP [4].

11.4 Conclusions

Since the initial description of retrolental fibroplasia, or ROP in 1942, a significant amount of advancements in the understanding of the pathophysiology of the disease, the incidence, risk factors, and treatment technologies have been made. Utilization of ablative laser photocoagulation in a nearly confluent manner continues to be the gold standard in the treatment of threshold and pre-threshold ROP when coupled with wide-angle photography to objectively evaluate skip areas. Unfortunately, the technicality of the procedure requires significant training and skill development, limiting the number of providers that are able to provide effective treatment. Pediatric retinal surgeons excel at laser technique and with early examinations and frequent monitoring, can prevent the development of complications and progression of disease.

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