Treatment of ROP

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In the late 1980s, a large multi-centered trial investigated the efficacy of cryotherapy for ROP (CRYO-ROP).

Infants weighing less than 1,251 grams were enrolled.

Approximately 66% of the infants developed ROP.

However, 6% of infants progressed to threshold disease.
At 15 years, the rate of unfavorable outcomes was 30% for treated eyes and 51.9% ($p < 0.001$) for eyes that were observed without cryotherapy.

Despite improved outcome with cryotherapy compared to observation, almost 45% of eyes had visual acuity less than 6/60 despite treatment.
Laser treatment for retinopathy of prematurity
Retinal ablation with laser photocoagulation has proven to be safe and at least as effective as cryotherapy in preventing unfavorable outcomes, with a rate of disease regression after treatment of 71–100%.

Furthermore, recent studies have reported that laser photocoagulation has superior visual acuity outcomes (20/33 versus 20/133; 20/66 versus 20/182) and ultimate refractive error (−6.50 D versus −8.25 D; −4.45 D versus −7.65 D) compared to cryotherapy.
Earlier treatment of eyes with high-risk, pre-threshold disease significantly reduced unfavorable visual outcomes from 19.8% to 14.3%, and decreased unfavorable anatomical outcomes from 15.6% to 9.0%.
### ET-ROP Surveillance/Treatment Grid

<table>
<thead>
<tr>
<th></th>
<th>Zone I</th>
<th>Zone II</th>
<th>Zone III</th>
<th>Zone I</th>
<th>Zone II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature</td>
<td></td>
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<tr>
<td>Stage 1</td>
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<td>Stage 2</td>
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<tr>
<td>Stage 3</td>
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</tbody>
</table>

- **Type I ROP - Treat**
- **Type II ROP - Wait/watch (screen 2x/week)**
- **Watch (screen 1x/week)**
- **Watch (screen every 2 weeks)**
Portable laser systems utilizing indirect ophthalmoscopy to administer laser treatment offer convenience and portability.

Laser choices for retinal ablation include either diode (810 nm) or argon green (514 nm), with the diode laser being associated with deeper absorption and a reduced risk of cataract induction.

Initial laser settings are often set at a power of 200–400 mW for 0.1–0.3 s, with a whitish-grey burn the desired result.
The density of laser retinal ablation for ROP may have a significant impact on the ability to control disease progression.

Confluent pattern resulting in a progression rate of 3.6%, significantly different from the less confluent pattern with a progression rate of 29.4%.
Complications of laser treatment for retinopathy of prematurity

- Undertreatment
- Overtreatment (retinal burns, retinal breaks, choroidal bleeding, exudative RD, vitreous hemorrhages)
- Corneal burns
- Iris burns
- Anterior segment hemorrhage
- Inflammation
- Anterior segment ischemia (resulting in corneal opacification, hypotony, pupillary membranes, cataract, or phthisis)
- Cataract
- Myopia
Anti-VEGF Therapy
Less Destructive
Easy Procedure
Less Refractive Error
Late Recurrence
Intra-Ocular and Systemic Side Effects
At 54 weeks postmenstrual age, 4% of eyes treated with intravitreal bevacizumab had recurrences, while 22% of eyes in the laser treatment group had recurrences. These results showed a significant difference between bevacizumab and laser ($p = 0.002$), with results significant for zone I disease ($p = 0.003$), but zone II disease failed to reach statistical significance ($p=0.27$).
COMPARISON OF INTRAVITREAL INJECTION OF RANIBIZUMAB VERSUS LASER THERAPY FOR ZONE II TREATMENT-REQUIRING RETINOPATHY OF PREMATURITY

GUOMING ZHANG, MD, PhD,* MINGMIN YANG, MD, MSc,* JIAN ZENG, MD,* GEORGIOS VAKROS, MBCI, B, MSc;† KANGJIN SU, MD,* MIAOHONG CHEN, MMSc,* HUILIN LI, MMSc,* RUYIN TIAN, MD,* NA LI, MD,† SONG TANG, MD,* HONGHUI HE, BN,* WENJING TAN, BN,* XIANGMEI SONG, MNurs,* RUNSEN ZHUANG, MSc§ SHENZHEN SCREENING FOR RETINOPATHY OF PREMATURITY COOPERATIVE GROUP

Purpose: To compare the efficacy of intravitreal injection of ranibizumab (IVR) monotherapy and laser therapy for treatment-requiring retinopathy of prematurity (ROP) in Zone II.

Methods: A prospective, randomized, controlled single-center trial was applied from January 2014 to December 2014; infants who were diagnosed as Zone II treatment-requiring ROP (i.e., Zone II Stage 2 or 3 ROP with plus disease) were randomly assigned to receive IVR monotherapy or laser therapy, and the follow-up interval was at least 6 months. Any eyes that developed recurrence of ROP underwent crossover re-treatment.

Results: A total of 100 eyes of 50 ethnic Han Chinese infants were enrolled. At the last follow-up, 26 eyes of 13 infants developed recurrence of ROP in the IVR group and 2 eyes of 1 infant developed recurrence of ROP in the laser therapy group. There was a significant statistical difference in the rate of ROP recurrence between IVR and laser therapy to treat Zone II treatment-requiring ROP ($P = 0.001$).

Conclusion: Although IVR appears to regress ROP to certain levels and continue to promote the vascularization of peripheral retinal vessels, a substantial proportion of infants developed recurrence of ROP after a single-dose IVR. Therefore, IVR is not recommended as a single-dose monotherapy for Zone II treatment-requiring ROP.

RETINA 0:1–8, 2016
Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity (Review)

Sankar MJ, Sankar J, Chandra P
### Analysis 1.1. Comparison I Anti-vascular endothelial growth factor therapy versus cryo/laser therapy, Outcome I Structural outcome - partial or complete retinal detachment.

**Review:** Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity

**Comparison:** 1 Anti-vascular endothelial growth factor therapy versus cryo/laser therapy

**Outcome:** 1 Structural outcome - partial or complete retinal detachment

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intravitreal bevacizumab n/N</th>
<th>Laser therapy n/N</th>
<th>Risk Ratio M-H;Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H;Fixed 95% CI</th>
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</thead>
<tbody>
<tr>
<td>1 Zone I</td>
<td></td>
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</tr>
<tr>
<td>BEAT-ROP Trial 2011</td>
<td>0/31</td>
<td>2/33</td>
<td>83.1 %</td>
<td>0.21 [0.01, 4.26]</td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>31</strong></td>
<td><strong>33</strong></td>
<td></td>
<td><strong>83.1 %</strong></td>
<td><strong>0.21 [0.01, 4.26]</strong></td>
</tr>
</tbody>
</table>

Total events: 0 (Intravitreal bevacizumab), 2 (Laser therapy)

Heterogeneity: not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

<table>
<thead>
<tr>
<th>2 Zone II</th>
<th></th>
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<tbody>
<tr>
<td>BEAT-ROP Trial 2011</td>
<td>2/39</td>
<td>0/40</td>
<td>16.9 %</td>
<td>5.13 [0.25, 103.45]</td>
<td></td>
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<tr>
<td>Karkhanem 2016</td>
<td>0/43</td>
<td>0/36</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Zhang 2016</td>
<td>0/25</td>
<td>0/25</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>107</strong></td>
<td><strong>101</strong></td>
<td></td>
<td><strong>16.9 %</strong></td>
<td><strong>5.13 [0.25, 103.45]</strong></td>
</tr>
</tbody>
</table>

Total events: 2 (Intravitreal bevacizumab), 0 (Laser therapy)

Heterogeneity: not applicable

Test for overall effect: Z = 1.07 (P = 0.29)

**Total (95% CI)** 138 134  100.0 %  1.04 [0.21, 5.13]

Total events: 2 (Intravitreal bevacizumab), 2 (Laser therapy)

Heterogeneity: Chi^2 = 2.16, df = 1 (P = 0.14); I^2 = 54%

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Chi^2 = 2.16, df = 1 (P = 0.14), I^2 = 54%
Surgical Management of Retinopathy of Prematurity
It mechanically reattaches the retina by counteracting the forces exerting traction on the retina.
Important drawbacks to scleral buckling which adversely affect the functional outcomes include lower anatomical success rates (60%-75%), need for a secondary procedure to divide or remove the encircling element and induction of severe myopia and anisometropia with the resulting risk of amblyopia.
Advantages of vitrectomy in stage 4 ROP include removing endogenous vasodilators and angiogenic factors such as vascular endothelial growth factor (VEGF) from the vitreous cavity in addition to releasing antero-posterior tractions.
Outcomes of vitrectomy in stage 4 ROP are more favorable (90% success with mean follow-up of 1 year) as compared to scleral buckling procedures.

Vitreoretinal surgery is usually employed for treatment of stage 5 ROP. Despite relatively acceptable rates of retinal reattachment, functional outcomes have been poor.
Long-term Outcomes on Lens Clarity after Lens-Sparing Vitrectomy for Retinopathy of Prematurity

Eric Nudleman, MD, PhD, 1 Joshua Robinson, MD, 2 Prethy Rao, MD, 3 Kimberly A. Drenser, MD, PhD, 3, 4 Antonio Capone, MD, 3, 4 Michael T. Trese, MD 1, 4

Objective: To describe the long-term effect of lens-sparing vitrectomy surgery for advanced retinopathy of prematurity (ROP) on lens clarity.

Design: Retrospective case series at a single tertiary referral pediatric vitreoretinal practice.

Participants: Four hundred ninety-six eyes from 351 patients were included.

Methods: A retrospective chart review was conducted of patients with diagnosis of ROP stage 4A, 4B, and 5 who underwent lens-sparing vitrectomy (LSV) between 1992 and 2013. Data were collected from patient charts, including gender, date of birth, gestational age at birth, birthweight, stage of ROP at presentation, initial treatment (laser or cryotherapy), date of LSV, date of lensectomy (if performed), lens status at time of lensectomy, date of last visit, lens status at last visit, subsequent retinal surgeries, and retinal attachment status at last visit. Patients were excluded if any surgery had been performed at an outside institution before referral, or if a scleral buckle had been placed. Eyes with a concurrent anatomic abnormality, such as coloboma or microcornea, or a known family history of familial exudative vitreoretinopathy (FEVR), were also excluded.

Main Outcome Measures: Retinal reattachment after LSV, lensectomy after LSV, lens opacity at the time of lensectomy, and lens clarity at last follow-up.

Results: Four hundred ninety-six eyes from 351 patients met inclusion criteria for this study. The reattachment rate after a single LSV surgery was 82.1% for stage 4A, 69.5% for stage 4B, and 42.6% for stage 5. Subsequent retinal surgeries were required in 19.8% of eyes, with 88.7% of them including a lensectomy. Among eyes requiring lensectomy, 75% occurred within the first year after LSV surgery. Lens opacities were present in 26.6% of eyes at the time of lensectomy. Of all eyes in this series, 5.9% required lensectomy because of lens opacity.

Conclusions: This study demonstrates that lens clarity is observed in most eyes after LSV surgery for advanced ROP for the patient’s childhood. Within the first decade of life, if necessary, lensectomy after LSV occurred mostly within 1 year following LSV. Ophthalmology 2015;122:755-759 © 2015 by the American Academy of Ophthalmology.
<table>
<thead>
<tr>
<th></th>
<th>Stage 4A</th>
<th>Stage 4B</th>
<th>Stage 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent attachment with single surgery</td>
<td>82.1</td>
<td>69.5</td>
<td>41.6</td>
<td>75.2</td>
</tr>
<tr>
<td>Percent lensectomy following LSV</td>
<td>12.5</td>
<td>29.4</td>
<td>57.5</td>
<td>22.3</td>
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<tr>
<td>Percent with lens opacity at time of lensectomy</td>
<td>17.1</td>
<td>29.4</td>
<td>26.0</td>
<td>26.6</td>
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<tr>
<td>Percent with lens opacity (total)</td>
<td>21.1</td>
<td>8.6</td>
<td>15.0</td>
<td>5.9</td>
</tr>
</tbody>
</table>

LSV = lens-sparing vitrectomy.
Thank You