Structural outcomes of eyes with threshold retinopathy of prematurity treated with laser therapy or cryotherapy

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Abstract

Aim: To determine the structural outcomes of threshold retinopathy of prematurity treated with laser photocoagulation or cryotherapy and to identify risk factors for retreatment and significant structural changes.

Patients and methods: This was a retrospective analysis of the medical records of infants with threshold retinopathy of prematurity treated with laser photocoagulation or cryotherapy from 1997 to 2002 with at least 6 months of treatment follow-up.

Results: Forty one eyes of 21 infants were treated for threshold retinopathy of prematurity during the study period. All eyes had zone II disease. Seven of the 41 eyes (17%) had significant structural changes, 6 eyes (15%) had moderate dragging of retinal vessels, 3 eyes (7%) had dragging of the optic disc, 1 eye (3%) had macular ectopia, and 1 eye (3%) had retinal pigment epitheliopathy of the macula. No patients had retinal detachment, macular fold, or retrolental tissue. Nine of 39 eyes (23%) needed retreatment, owing to either persistence (7 eyes) or recurrence (2 eyes) of threshold disease. Cryotherapy appeared to be more likely to result in significant anatomic changes but was less prone to result in retreatment.

Conclusions: No infant had an unfavorable anatomic outcome defined by the Cryotherapy for Retinopathy of Prematurity Cooperative Group study. This result may be attributed to the absence of zone I disease in the patients in this study, advances in neonatology, change in treatment modality, and increasing experience with treatment. Laser treatment and cryotherapy are safe and effective for the treatment of threshold retinopathy of prematurity and their roles are not mutually exclusive. Each modality has its advantages and disadvantages, but they can act together to achieve good structural and functional outcomes.

Key words: Cryotherapy, Lasers, Retinopathy of prematurity

Introduction

The Cryotherapy for Retinopathy of Prematurity (Cryo-ROP) Cooperative Group study demonstrated that cryoablation of the peripheral avascular retina reduced the incidence of an unfavorable outcome for infants with threshold retinopathy of prematurity (ROP) in treated versus control eyes (47.1% vs 61.7% for visual acuity and 26.9% vs 45.4% for fundus status). The benefit of cryoablation was maintained for 10 years in a long-term follow-up study. Despite the improvement for eyes with ROP, cryotherapy still has potential adverse effects, including intraoperative bradycardia and apnea. Conjunctival laceration, vitreous hemorrhage, and swelling of the lids and conjunctiva are common postoperative complications.
Since 1990, retinal photocoagulation with transpupillary laser (argon or diode laser) has rapidly gained acceptance by ophthalmologists treating patients with ROP. Studies comparing laser and cryotherapy for the treatment of ROP have found equal efficacy for these 2 modalities, but with fewer complications reported for laser treatment.\(^6\)\(^7\) However, the change to laser therapy has coincided with many advances in prenatal and neonatal care, including the use of exogenous surfactant, administration of perinatal corticosteroids, and improved parenteral nutrition, all of which may improve the ocular outcome independently of the retinal treatment strategy.

The primary objective of this study was to compare the structural outcomes of 41 eyes of 21 patients with threshold ROP treated with laser or cryotherapy between 1997 and 2002. The potential risk factors for the failure of primary treatment and the development of significant structural outcomes were identified.

**Patients and methods**

The hospital and outpatient records of all patients who developed threshold ROP at Tuen Mun Hospital between January 1997 and December 2002 were retrospectively reviewed. Most of the screening and treatment was performed by 1 ophthalmologist and the remainder was performed under supervision by the unit retinal specialist. The stages and location of ROP were recorded according to the international classification of ROP.\(^8\) Threshold disease was defined as a minimum of 5 contiguous or 8 cumulative clock-hours of stage 3 ROP in the presence of plus disease. Significant structural changes specified in this report include unfavorable anatomic outcomes defined by the Cryo-ROP study (presence of retinal detachment, macular fold, or retrolental tissue),\(^9\) significant temporal dragging of the retinal vessels, dragging of the optic disc, macular ectopia, and retinal pigment epitheliopathy of the macula.

After the threshold ROP was noted, treatment was administered within 72 hours. Argon or diode laser treatment was the first choice of intervention and was performed in the neonatal intensive care unit using topical anesthesia (0.3% benoxinate) together with oral (chloral hydrate) or intravenous (midazolam) sedation, with an attending neonatologist standing by. The pupils were dilated with 0.5% cyclopentolate and 2.5% phenylephrine. Laser burns spaced 1.0 to 0.5 burn-width apart were applied throughout the avascular retina and the peripheral region was approached via the indentation method. The power used was sufficient to produce a dull gray/white reaction. Cryotherapy was chosen as the initial treatment for patients with small pupil or decreased media clarity, or in cases of laser machine failure. Cryotherapy was administered under general anesthesia in the operating theater and was applied continguously to the entire circumference of the avascular retina anterior to the edge of the ridge. All infants were examined for any signs of deterioration or regression within 1 week of treatment.

The indications for retreatment included the presence of untreated (skipped) areas and the persistence of plus disease in association with any of the following characteristics:

- segmental shallow retinal detachment (which suggested continued adjacent disease activity) in the areas skipped
- progression of extraretinal fibrovascular proliferation (increasing floridity of the ridge) contiguous with a skipped area\(^9\)
- recurrence after a period of regression.

When any of these characteristics were noted, retreatment was performed as soon as possible. Cryotherapy or laser applications were made only to previously untreated avascular retina in sectors of continued activity. The choice of cryotherapy or laser was dependent on whether the skipped areas were located anteriorly or posteriorly, respectively.

Data collected from eligible patients included sex, race, gestational age, birth weight, postconceptional age at treatment, duration of follow-up, zone, and clock-hours of threshold disease. Oxygen saturation level was not included in the data collection. Treated eyes were excluded if any of the above data were omitted from the records, or if follow-up had been performed for less than 6 months.

Non-parametric statistics were used because of the small sample size. A p value of 0.05 or less was considered significant. Owing to the small number of eyes in the study, the lack of statistical significance for a test should be viewed with caution.

**Results**

Forty one eyes of 21 infants were included in this study and all of them were Chinese. One patient was treated with laser in 1 eye only and the fellow eye did not require therapy. There were 7 girls and 14 boys. The mean birth weight was 822 g (Table 1 and Figure 1), and the mean gestational age was 26.4 weeks. Chronologic age at treatment ranged from 7 to 15 weeks (postconceptional age, 33 to 41 weeks). The mean duration of follow-up was 30 months (range, 7 to 64 months). All patients had zone II disease and further subdivision into anterior, mid-, or posterior zone II was not attempted. Five of the 21 patients were twins. All infants were naturally conceived. Sixteen patients had a birth weight of less than 1000 g (Figure 1), meaning that 86% were in the

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of 21 patients (41 eyes) undergoing treatment for threshold retinopathy of prematurity.</th>
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</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
</tr>
<tr>
<td>Duration of follow-up (months)</td>
</tr>
<tr>
<td>Postconceptional age at treatment (weeks)</td>
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<tr>
<td>Clock-hours of stage 3 retinopathy of prematurity</td>
</tr>
</tbody>
</table>
extreme low birth weight group. However, the frequency of retreatment did not appear to relate to decreasing birth weight.

**Treatment safety**

All patients experienced transient lid swelling, conjunctival injection, and chemosis, but no other immediate postoperative ocular complications were noted. One patient receiving laser therapy who had bradycardia and apnea required only brief interruptions (<5 minutes). Only 1 procedure had to be aborted in the laser therapy group due to machine failure.

**Treatment efficiency**

The efficiency of laser therapy or cryotherapy was assessed by recording the number of eyes needing retreatment. Two eyes (patient 11) were excluded, as the reason for retreatment was laser machine failure (Table 2). The other 39 eyes were divided into a laser therapy group (26 eyes) and cryotherapy group (13 eyes). The underlying reason for performing initial cryotherapy instead of laser was the presence of small pupils; no significant vitreous hemorrhage or cataract was

![Figure 1. Birth weight of infants with retinopathy of prematurity.](image)

![Table 2. Summary of treatment modality, retreatment, and structural outcomes.](table)
found. As shown in Table 3, there was no statistically significant difference in birth weight and gestational age between the 2 groups. Overall, 9 of 39 eyes (23%) needed retreatment because of the non-regression of threshold ROP (7 eyes) or recurrence of threshold ROP (2 eyes).

Of the 26 eyes initially treated with laser, 7 eyes (27%) needed retreatment with cryotherapy (6 eyes) or laser (1 eye). The mean number of laser burns was 859 ± 202 (range, 600 to 1383 burns). The power and duration of the laser burns ranged from 0.22 to 0.80 watts and 0.10 to 0.15 seconds, respectively. Comparison of the characteristics of the successful initial laser treatment group and the group that needed retreatment is shown in Table 4. The 2 groups did not show any statistically significant differences in birth weight, gestational age, and number of laser burns that could account for the failure of primary treatment. Thirteen eyes were initially treated with cryotherapy, of which 2 (15%) needed retreatment with laser.

**Treatment effectiveness**

Effectiveness was assessed by fundus examination for any significant structural changes noted at the last follow-up. Table 2 shows that 7 of 41 eyes (17%) had at least 1 type of significant structural outcome. Of the 11 eyes treated with cryotherapy only, 4 eyes (36%) had significant structural changes. Among the 30 eyes initially treated with laser or undergoing retreatment laser, 3 (10%) had significant structural changes — 1 of the eyes was initially treated with laser, and the other 2 were being retreated.

Figure 2 shows the relationship between the treatment method and structural outcomes. Significant anatomic changes included dragging of retinal vessels (6 eyes; 15%), optic disc dragging (3 eyes; 7%), macular ectopia (1 eye; 3%), and macular retinal pigment epitheliopathy (1 eye; 3%). No eyes had any unfavorable anatomic outcome defined by the Cryo-ROP study.

**Discussion**

191 premature infants (birth weight ≤1500 g or gestational age ≤31 weeks) underwent screening for ROP between 1997 and 2002 at Tuen Mun Hospital. The mean birth weight was 1216 ± 313 g (range, 550 to 2200 g) and the mean gestational age was 29.40 ± 2.64 weeks (range, 23.6 to 38.2 weeks). Twenty one infants (11%) developed threshold ROP, which was a higher incidence than 4.0% to 8.2% in other studies. Factors that may contribute to the differences in the incidence of ROP between centers include different inclusion criteria, neonatal survival, and ethnic mix. The diagnoses made by individual clinicians may also vary, although this would be less for severe disease.

The birth weight and gestational age in this study were similar to those reported in the Cryo-ROP study (822 ± 155 g vs 800 ± 165 g and 25.4 ± 1.4 weeks vs 24.5 ± 1.4 weeks). The mean number of clock-hours of stage 3 disease was slightly lower in this study than in the Cryo-ROP study (7.3 clock-hours vs 9.6 clock-hours). The retreatment rate (23.0%) was comparable to that of other series (7.0% to 35.5%).

Laser therapy has been the first choice of treatment at Tuen Mun Hospital since 1997. It is generally seen as being at

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Table 3. Comparison of mean birth weight and gestational age between patients receiving laser therapy and those receiving cryotherapy.

<table>
<thead>
<tr>
<th></th>
<th>Laser therapy</th>
<th>Cryotherapy</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes</td>
<td>26</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Birth weight (± SD; range) [g]</td>
<td>815 ± 158 (550-1070)</td>
<td>849 ± 158 (625-1070)</td>
<td>0.529</td>
</tr>
<tr>
<td>Gestational age (± SD; range) [wk]</td>
<td>26.3 ± 1.3 (24.6-29)</td>
<td>26.9 ± 1.6 (24.9-29.3)</td>
<td>0.242</td>
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</table>

Table 4. Comparison between patients receiving successful initial laser therapy and patients needing retreatment.

<table>
<thead>
<tr>
<th></th>
<th>Successful initial therapy</th>
<th>Retreatment</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes</td>
<td>19</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Birth weight (± SD; range) [g]</td>
<td>795 ± 172 (550-1070)</td>
<td>867 ± 103 (795-1070)</td>
<td>0.194</td>
</tr>
<tr>
<td>Gestational age (± SD; range) [wk]</td>
<td>26.1 ± 1.3 (24.6-29.0)</td>
<td>26.7 ± 1.3 (25.0-28.4)</td>
<td>0.298</td>
</tr>
<tr>
<td>Number of laser burns</td>
<td>830 ± 210 (600-1383)</td>
<td>936 ± 167 (800-1127)</td>
<td>0.184</td>
</tr>
</tbody>
</table>

Figure 2. Treatment method and structural outcomes of infants with retinopathy of prematurity.
least as effective as cryotherapy, and the advantages of laser therapy over cryotherapy have been well documented. The infants in this study received a similar mean number of laser burns (859) to those in other studies who were treated with a similar scatter pattern (508 to 1200 burns). There were no significant differences in birth weight, gestational age, or number of laser burns with respect to the success or the failure of laser treatment. The frequency of retreatment following cryotherapy (15%) was lower than that following laser therapy (27%). The higher failure rate for laser therapy may be due to the following factors:

- initial learning curve for laser therapy
- infant handling and inadequate sedation may cause difficulty in applying the laser to zone II
- better ablation effect of cryotherapy, especially in areas of poor media clarity and in the more anterior avascular zone II.

To reduce the frequency of retreatment for the laser group, the following options are suggested:

- apply laser in a near-confluent pattern, where laser spots are less than 1 burn width apart — this has been shown to prevent the progression of disease and limit the need for retreatment
- treat the patient simultaneously with laser applied to the posterior retina and cryotherapy to the anterior retina under general anesthesia — this provides greater technical ease, shorter treatment duration, and perhaps decreases the risk of cataract or anterior segment ischemia.

The anatomic outcomes of the patients in this study were better than those reported in the Cryo-ROP study at the 1-year follow-up. None of the eyes in this study had an unfavorable outcome, compared with 26% of patients recorded in the Cryo-ROP study, and 7% to 12% recorded in other studies of laser treatment for threshold ROP. The reason for this difference could be the fact that all the eyes in this study had zone II disease. As shown in the Cryo-ROP study, zone II disease results in fewer unfavorable outcomes in both treated and control eyes when compared with zone I disease.

Dragging of temporal vessels (14.6%) was the most common structural change found in this study. However, this rate was lower than that of other studies (22% to 28%). This may reflect better future functional outcomes, as absence of dragging has been shown to be a predictor of good visual acuity in both laser-treated and cryotherapy-treated eyes. Cryotherapy-treated eyes were more likely to develop significant structural changes in this study and in other studies. However, there were no significant differences in birth weight and gestational age between the laser and cryotherapy groups to account for this trend. This result may be secondary to the small pupils in the cryotherapy-treated eyes, which may imply more active plus disease or non-selective damage of cryotherapy to non-target tissues such as the sclera and choroids.

The improvement shown in the results of this study may be attributable to the change in treatment modality and an effect of increasing experience with this treatment. The authors also speculate that the advances in prenatal and neonatal care such as the use of surfactant and administration of maternal steroids during pregnancy, as well as improved parenteral nutrition might promote improved ocular outcomes independent of the retinal treatment strategy.

Since the follow-up period was shorter than that in other reported studies related to anatomic outcomes after laser treatment, it is possible that further significant structural changes may occur as the eyes continue to develop. The anatomic and functional outcomes could be further analyzed with a longer follow-up period.

Conclusions

This study suggests that laser treatment with topical anesthesia and sedation for threshold ROP is safe, efficient, and effective when compared with the Cryo-ROP study and other laser treatment studies. Eyes undergoing cryotherapy may be at greater risk for significant structural changes, especially induced myopic shift, when compared with laser-treated eyes. However, eyes treated with laser may have a higher incidence of retreatment, as indicated in this study. The authors suggest that cryotherapy and laser be performed together as the initial choice of treatment for threshold ROP with anterior disease or poor fundal visibility. This approach provides the complementary advantages of each modality while tempering the disadvantages of each, thus helping to avoid missed ischemic areas, reducing the frequency of retreatment, and minimizing later structural distortions.

References


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