Dexamethasone Eye Drops for the Treatment of Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a leading cause of preventable childhood blindness. It is classified and typed according to international guidelines.1

Frequent follow-up warranted for type 2 ROP

(1) Zone I: stage 1 or 2 ROP without plus disease;
(2) Zone II: stage 3 ROP without plus disease.

Indication for treatment for type 1 ROP

(1) Zone I: all stages of ROP with plus disease;
(2) Zone II: stage 3 ROP with or without plus disease;
(3) Zone II: stage 2 or 3 ROP with plus disease.

Studies on both animals and humans have demonstrated the role of inflammatory mediators in the retinopathy process.2,3 Dexamethasone is a glucocorticoid with a known reductive effect on several of these mediators and on the expression of vascular endothelial growth factor (VEGF).4

Beginning in 2016, infants receiving laser ablation for type 1 ROP at Skåne University Hospital were administered dexamethasone (1 mg/ml) eye drops postoperatively, usually 3 times daily. None of the infants receiving postoperative topical steroids needed retreatment, compared with a general retreatment frequency of 26% nationally when postoperative dexamethasone was not routinely administered.5

During 2018 and 2019, 2 premature infants were started on a dexamethasone regimen before planned laser treatment was performed. In 1, the laser treatment could be postponed, and in the other, the laser treatment was cancelled. Successively, several other infants with type 2 ROP who were considered to be at very high risk of requiring laser ablation were administered dexamethasone drops preoperatively, and regression of ROP changes was observed on multiple occasions. Consequently, all infants born in 2020 with type 2 ROP were administered dexamethasone drops before laser treatment, but usually in a lower dosage of 1 drop daily.

We, therefore, aim to compare treatment frequency for screened infants born between 2016 and 2020 in the southern health care region of Sweden by conducting a systematic retrospective analysis comparing dexamethasone-treated and untreated infants.

This retrospective study was conducted in accordance with the Declaration of Helsinki, and it received ethical approval from the Swedish ethical board. The study followed the Strengthening and Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

All screened children born between 2016 and 2020 in the southern health care region of Sweden were included. They were screened according to national guidelines: all infants born between 2016 and 2019 at a gestational age of <31 weeks were included, and all infants born in 2020 at a gestational age of <30 weeks, because of new guidelines, were included.7 The infants were classified and typed according to international guidelines.1

Forty-eight infants were diagnosed with type 2 ROP and were further analyzed and compared in terms of their birth years. During the early years, screening was performed using either indirect ophthalmoscopy or digital wide-field photography (RetCam Shuttle, Natus Medical Inc.). All infants who were administered dexamethasone drops preoperatively were examined at each screening visit using digital wide-field photography by a pediatric ophthalmologist. The photographs were discussed with an experienced pediatric ophthalmologist (L.G.), who also performed laser ablation when needed, to reach a consensus on the appropriate treatment strategy at each occasion. During the entire time period, all infants were preoperatively examined using digital wide-field photography to confirm the presence of type 1 ROP before any laser treatment was performed.

To compare the frequency of infants progressing from type 2 to type 1 ROP among dexamethasone-treated and untreated infants, an odds ratio with a 95% confidence interval was calculated using binary logistic regression. Univariate and multivariate analyses were performed. Significance level was set at P < 0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences software (IBM statistics for Macintosh, version 26.0, IBM Corporation).

A total of 763 preterm infants were screened (Table S1 available at www.ophthalmologyretina.org). One child was excluded because of death between the time of type 2 ROP diagnosis and the determination of the need for laser ablation. Overall, 48 infants with type 2 ROP were included in the analyses, of whom 31 did not receive any dexamethasone eye drops before laser ablation and 17 received dexamethasone eye drops when type 2 ROP was diagnosed. Of the 17 infants, 16 had stage 3 in zone 2 and 1 had stage 2 in zone 1, all without plus disease.

The photographs obtained from an infant treated with dexamethasone are displayed in Figure S1 (available at www.ophthalmologyretina.org). Table S2 (available at www.ophthalmologyretina.org) presents the characteristics and comorbidities among dexamethasone-treated and untreated infants. As evident from Table 1, the treatment frequency among infants with type 2 ROP who did not receive dexamethasone before laser ablation was 74%, compared with 24% among infants who did receive dexamethasone eye drops for type 2 ROP. The odds ratio between the dexamethasone-treated and untreated infants was 0.11 (95% confidence interval, 0.03–0.43; P = 0.001) in the univariate analysis. Of the other possible covariates in Table S2, only bronchopulmonary dysplasia affected the results, and in the multivariate analysis, the odds ratio increased to 0.19 (95% confidence interval, 0.04–0.84; P = 0.03).

The treatment frequency was initially 3 times daily (7 infants) but was successively lowered to an initial dosage of twice daily...
is a key factor in the development of ROP changes. The results corroborate our option for type 2 ROP. A randomized study is warranted to previous studies on the use of steroid eye drops as a treatment of this pilot study further support this idea. We have not found any the results indicate that such eye drops can prevent these infants some eye drops were introduced for the treatment of type 2 ROP, treatment would make a monumental difference for those individuals. developing and prevent blindness, this simple and low-cost treat-
drops for infants with type 2 ROP can forestall type 1 ROP from close follow-up scheme are not feasible. If treatment with steroid laser treatment are not available and anti-VEGF injections with a
null hypothesis with this difference between the groups.
set at 0.05, a total of 28 infants would be required to reject the

<table>
<thead>
<tr>
<th>Total</th>
<th>21</th>
<th>27</th>
<th>48</th>
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</thead>
<tbody>
<tr>
<td>Dexamethasone-treated infants, n (%)</td>
<td>13 (76)</td>
<td>4 (24)</td>
<td>17</td>
</tr>
<tr>
<td>Untreated infants, n (%)</td>
<td>8 (26)</td>
<td>23 (74)</td>
<td>31</td>
</tr>
<tr>
<td>No Laser Ablation</td>
<td>Laser Ablation</td>
<td>Total</td>
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(3 infants) and then once daily (7 infants). The dosage was gradually tapered off, with the final dosage being every other day before treatment ended. The median time for infants on dexamethasone who did not need laser treatment was 28 days, ranging from 14 to 98 days. The median postnatal age when dexamethasone drops were initiated was 10.5 weeks, ranging from 7.1 to 12.7 weeks. The advantages of this study were that all screened preterm infants in the southern health care region of Sweden were included. Although it was a retrospective analysis, we selected a time period during which the recommended saturation levels remained unaltered. All infants with type 2 ROP who received dexamethasone drops were examined using digital wide-field photography and assessed by an experienced pediatric ophthalmologist (L.G.). Several previous studies have demonstrated that inflammation is a key factor in the development of ROP changes. The results of this pilot study further support this idea. We have not found any previous studies on the use of steroid eye drops as a treatment option for type 2 ROP. A randomized study is warranted to corroborate our findings. With a power of 0.8 and type 1 error set at 0.05, a total of 28 infants would be required to reject the null hypothesis with this difference between the groups. In many countries and remote areas, neonatal anesthesia and laser treatment are not available and anti-VEGF injections with a close follow-up scheme are not feasible. If treatment with steroid drops for infants with type 2 ROP can forestall type 1 ROP from developing and prevent blindness, this simple and low-cost treatment would make a monumental difference for those individuals. With a sharp decline in treatment frequency when dexamethasone eye drops were introduced for the treatment of type 2 ROP, the results indicate that such eye drops can prevent these infants from developing type 1 ROP to a large extent.

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**HUMAN SUBJECTS:** This study received ethical approval from the Swedish ethical board. All research adhered to the tenets of the Declaration of Helsinki.

No animals were used in this study.

**Abbreviations and Acronyms:**

**ROP** = retinopathy of prematurity; **VEGF** = vascular endothelial growth factor.

**Keywords:**

retinopathy of prematurity, dexamethasone, inflammation, type 2 ROP, type 1 ROP.

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**References**