Original article

**Diode laser photocoagulation of retinopathy of prematurity**

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**ARTICLE INFO**

**Article history:**
Received 10 November 2010
Accepted 4 April 2011
Available online 21 March 2012

**Keywords:**
Retinopathy of prematurity
Retinal photocoagulation
Diode laser

**ABSTRACT**

Objective: To describe diode laser photocoagulation results in retinopathy of prematurity (ROP) in our hospital.

Material and method: Retrospective cross-sectional study based on clinical histories of the premature infants treated during the period from 2004 to 2008.

Results: In the treated group we found a predominance of pre-threshold retinopathy versus threshold retinopathy (84.35% vs 15.65%). The anatomic results were good in 96.5% of 147 eyes. None of the treated eyes in pre-threshold stage showed a poor result. Nine months after treatment, 84.85% of 132 eyes showed good functional results. A poor visual response was associated in most of the cases with neurological diseases. Infants with intraventricular hemorrhages had the worst anatomical and functional results. Strabismus (23.5%) and nystagmus (10.3%) rates were high, probably due to the increased prevalence of neurological diseases. The mortality rate in treated children was 7.3%.

Conclusions: Diode laser photocoagulation in ROP offers very good anatomical results when performed at the appropriate time. Nevertheless, prematurity is still a very important cause of visual dysfunction in infancy due to the associated neurological disturbances.

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**FOTOCOAGULACIÓN CON LÁSER DE DIOIDO EN LA RETINOPATÍA DEL PREMATURO**

**RESUMEN**

Objetivo: Describir los resultados de la fotocoagulación con láser de diodo en la retinopatía del prematuro (ROP) en nuestro hospital.


Resultados: La población tratada tiene un predominio de la retinopatía preumbral frente a retinopatía umbral (84,35 vs. 15,65%). Los resultados anatómicos fueron buenos en el 96,5% de 147 ojos. Ningún ojo tratado en fase preumbral tuvo mal resultado anatómico. A los 9 meses del tratamiento, los resultados funcionales fueron buenos en un 84,85% de 132 ojos. La mala respuesta visual se asoció en la mayoría de los casos a enfermedad neurológica.

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Introduction

The first technique that demonstrated its efficacy in the treatment of retinopathy of prematurity (ROP) was the ablation of the avascular peripheral retina with cryotherapy. The Multicenter trial of cryotherapy for retinopathy of prematurity (CRYO-ROP) achieved a reduction of unfavorable results in threshold retinopathy using cryotherapy, and these results stood for 10 years. Subsequently, diode laser began to be used for destroying the avascular retina. In 2002, the Early treatment for retinopathy of prematurity cooperative group (ETROP) demonstrated better results applying laser treatment in a less involved stage of the disease, known as high risk pre-threshold retinopathy. This prompted the American Pediatric Academy and the American Association of Pediatric Ophthalmology and Strabismus to publish recommendations for ROP exploration and treatment in 2006. In Spain, the Spanish Pediatric Association and the Spanish Neonatology Society have also published this type of recommendations.

This paper reviews the results of diode laser photoacogulation in the treatment of ROP in our center.

Subjects, material and methods

A transversal and retrospective study based on clinical record data covering a period of 5 years, from January 1, 2004 to December 31, 2008. Overall, 98 premature babies were photoacoagulated, 83 of them born in our hospital and 15 referred from other centers. One case of an atypical ROP in a baby born within term was excluded, as well as eyes with slight retinopathy which was not secondary to treatment and which were photoacoagulated in the same surgery as the opposite eye in which laser was indicated. Finally the study also excluded the eyes treated with a degree of retinopathy in which the treatment was not yet indicated, about to be released from hospital and those with doubtful follow-up after release. Accordingly, the study comprised 88 bilateral cases and 6 unilateral cases totaling 182 eyes treated following currently accepted indications.

The study recorded demographic data and associated morbidity. The ROP characteristics were established on the basis of the classification proposed by the International Committee for the Classification of Retinopathy of Prematurity. It also differentiated between threshold and pre-threshold retinopathy as well as the age at which the laser treatment was carried out, the number of sessions applied and the complications that arose.

Following the model utilized by ETROP, the results were observed at month 3 and 9 after treatment. As the treatment was performed between 2 and 3 months of age, the infants had an age between 5–6 and 11–12 months when their data were recorded. The checkup in month 3 only took into account the anatomic results. The study considered that a good anatomic result was when the retinopathy regressed completely, the posterior pole retina remained applied and the only visible alterations in the ocular fundus were the laser scars. Any other circumstance was taken as a poor result.

As for the nine-month checkup, in addition to the anatomic result the ocular alignment was assessed together with the presence of nystagmus and an estimation of the visual function. Due to the absence of a specific method to measure visual acuity in babies, for example the preferential gaze test, the ophthalmologist assessed the response to toys or a light source and recorded the results as good, doubtful or absent. In case of nystagmus, the assessment was binocular and in all other cases first occluding one eye and then the other. In some babies refraction was performed under cycloplegia, which was included in the study while in others it was carried out at later age and was not included in the study.

Finally, the follow-up losses were recorded as well as exits and their courses. A descriptive statistical analysis of the data was carried out, representing qualitative variables by absolute and relative frequencies, and the quantitative variables by means and standard deviation, with a CI of 95%.

The statistical data were processed with the SPSS 18.0.2 software.

Results

Table 1 shows the number of treated infants on the basis of their year of birth and mean gestational age and weight at birth.

Of the 94 infants of the study we have valid data for the three-month checkup of 76 because 6 died, while for other 12 we have data only up to hospital release. The study included both eyes in 71 cases and one eye in 5 cases, totaling 147 eyes included in the study.

Table 2 summarizes the demographic and associated morbidity characteristics of the 76 infants. There is a small prevalence of females over males (40/36). The gestational age ranged between 24 and 33 weeks, with a mean of 27.9 ± 2.25. Weight at birth ranged between 550 and 1901 g, with a mean of 1017 ± 262.
Table 1 – Number of infants treated per year of birth, with mean gestational age and weight at birth.

<table>
<thead>
<tr>
<th></th>
<th>2004 (n = 10)</th>
<th>2005 (n = 18)</th>
<th>2006 (n = 21)</th>
<th>2007 (n = 27)</th>
<th>2008 (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, weeks</td>
<td>26.6 ± 2.01</td>
<td>27.3 ± 1.91</td>
<td>28.3 ± 2.13</td>
<td>28.7 ± 2.39</td>
<td>26.7 ± 2.04</td>
</tr>
<tr>
<td>Weight at birth, g</td>
<td>966 ± 215.25</td>
<td>931 ± 243.12</td>
<td>1069 ± 310.94</td>
<td>1071 ± 234.09</td>
<td>894 ± 213.21</td>
</tr>
</tbody>
</table>

Table 2 – Demographic data and associated morbidity of infants.

<table>
<thead>
<tr>
<th></th>
<th>No. = 76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>47.4% (36)</td>
</tr>
<tr>
<td>Females</td>
<td>52.6% (40)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>27.6% (21)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>27.9 ± 2.25</td>
</tr>
<tr>
<td>Confidence interval 95</td>
<td>27.4–28.4</td>
</tr>
<tr>
<td>Weight at birth, g</td>
<td>1017 ± 262.7</td>
</tr>
<tr>
<td>Confidence interval 95</td>
<td>957.5–1077.6</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td></td>
</tr>
<tr>
<td>Incubator</td>
<td>5.3% (4)</td>
</tr>
<tr>
<td>CPAP</td>
<td>1.3% (1)</td>
</tr>
<tr>
<td>Assisted ventilation</td>
<td>93.4% (71)</td>
</tr>
<tr>
<td>Persistent arterial ductus</td>
<td>52.6% (40)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>30.39% (23)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>19.7% (15)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>67.1% (51)</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>90.8% (69)</td>
</tr>
<tr>
<td>Insulin therapy</td>
<td>44.7% (34)</td>
</tr>
</tbody>
</table>

The mortality rate in treated infants was of 7.3%. The exitus levelus group comprised 5 males and one female with a gestational age of 26 weeks and weight at birth of 885 g, the causes of death being bronchopulmonary dysplasia and septic shock.

Table 3 illustrates the retinopathy characteristics in the 147 treated eyes. There is a clear prevalence of pre-threshold retinopathy (84.3%) over threshold retinopathy (15.6%). Only 2 cases had ROP localized in area I. The most frequent indication was ROP grade 2 with plus in posterior pole located in area II and with an extension of 360°. There also was one bilateral case of what Serra defined as “post-threshold”, i.e. grade 3 plus with high prominence of neovascularization towards the vitreous or indications of fibrotic changes in neovascular formation, which usually are highly evolved cases even though the retina detachment has not occurred yet.

The age in which the infants received laser treatment ranged between 33 and 44 weeks (gestational age), with a mean of 36.7 weeks. The period between birth and treatment was on average 8.8 weeks. A single session was enough for 89.5% of children (68), although 8 infants (10.5%) required a second session and in 2 eyes additional cryotherapy was also applied.

The post laser complication rate was of 9.5% (14 eyes) which were resolved without significant sequels (Table 4).

The group made up by 12 treated infants with follow-up under 3 months exhibited characteristics similar to those of the remaining 76 and their immediate evolution up to hospital release was good, with complete remission of the retinopathy.

The anatomic results at month 3 post-treatment was good in 142 eyes (96.5%) and poor in 5 (3.5%), including one eye with a cup-shaped fold, two with macular ectopia and a further two with macular traction signs but with the macula remaining in place.

Between month 3 and 9 of the follow-up period, 8 infants were lost. The results at month 9 are based on the data of 68 infants and 132 eyes because in 4 infants only one eye was included. The ocular fundus appearance remained unaltered between the first and second checkup. Of the 68 infants, 76.5% (52) exhibited orthophoria, 23.5% (16) strabismus and 10.3% (7) nystagmus. The visual response was good in 84.85% (112) of treated eyes and doubtful or poor in 15.15% (20).

The number of eyes with poor visual results was higher than the number of eyes with poor anatomic results. We believe this could be due to the neurological disease...
ventilation in 93.4% of cases and exhibiting a significant part of known risk factors for the appearance and development of ROP. In general, these are severe diseases that could require aggressive treatments, surgical interventions and could even be lethal. In fact, the mortality rate (7.3%) is higher than the overall Neonatology Unit rate.

The mean age at which the infants were treated was of 36 weeks. None of the infants were treated before 33 weeks. At the other end, one baby was treated at 44 weeks because his general condition (enterocolitis, sepsis, meningitis, etc.) did not allow it earlier.

The publication of ETROP produced changes in treatment indications. For this reason, in our series and after said publication there is a clear predominance of pre-threshold retinopathy with 84.35% of eyes. With these indications, we achieved 96.5% of good anatomic results. In Spain and following said criteria, González Viejo et al. obtained 96.2% of good results, with a mean weight at birth of 1015 g and a gestational age of 27.9 weeks, identical to ours. In turn, Serra published 88.2% of overall good anatomic results but including all the ROP forms. If only the pre-threshold ROP group is considered, which would be similar to our study, said percentage rises to 97.3%. In said study, the mean gestational age was of 27.2 weeks and the mean weight at birth of 899 g, something below our study. In ETROP, the high risk pre-threshold retinopathy group (which would be most similar to our own) had 9.1% of unfavorable structural results, although the infants included in that study had a weight at birth of 703 g and a gestational age of 25.3 weeks (which is below our study) and also included more eyes with retinopathy in area I (40%) that had worse prognosis and accordingly a comparison between both results would not be valid.

When analyzing infants with poor anatomic results, we found that in 2 the photocoagulation was performed too late. The other 2 were very immature, with very low weight at birth, prolonged mechanical ventilation with severe associated morbidity. They were photocoagulation at the right time but the evolution was poor.

All the eyes with poor anatomic results belong to the threshold or post-threshold retinopathy group. There was none in the pre-threshold group with a poor result, which suggests that it is better not to wait for the disease to reach the threshold to treat. Against this approach it could be said that there are cases of pre-threshold disease that improve spontaneously. According to ETROP, one third of high-risk pre-threshold ROP cases that were allowed to evolve did not reach the threshold great and therefore did not require treatment. Therefore, it is necessary to develop strategies to help us decide whether to treat or to wait. Our criterion is based on the general condition of the infant (extreme prematurity, extended mechanical ventilation, intraventricular hemorrhage, etc.) and on the retinopathy characteristics. If the crest is located more posteriorly, the avascular retina is more extended or the posterior pole plus is more intense, all these are factors that lead us to decide for treatment. Villegas Becerril et al. found that serum levels of IGF-I and VEGF can be utilized as predictors of ROP severity, but the determination of said cytokins is not routine practice in hospitals for the time being. The algorithm proposed by Hellström seems more practical as it is based on weight gain in the first weeks

Exhibited by these infants. We researched this result analyzing the results of infants with intraventricular hemorrhage (IVH) (Tables 5 and 6).

Refraction under cycloplegia was only recorded in 45 infants, comprising 90 eyes. The distribution was of 36.7% emmetrope, 36.7% hypermetrope and 26.6% myopic. In addition, Table 7 shows the refractive results on the basis of the presence of intraventricular hemorrhage (Table 7).

### Table 6 - Percentage of poor visual and anatomic results at month 9 post-treatment comparing infants with and without intraventricular hemorrhage, assessing right and left eyes separately.

<table>
<thead>
<tr>
<th></th>
<th>With IVH (21)</th>
<th>Without IVH (45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor VR, RE</td>
<td>42.9% (9)</td>
<td>4.4% (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poor VR, LE</td>
<td>33.3% (7)</td>
<td>4.4% (2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Poor anatomic result RE</td>
<td>9.5% (2)</td>
<td>2.2% (1)</td>
<td>0.236</td>
</tr>
<tr>
<td>Poor anatomic result LE</td>
<td>4.8% (1)</td>
<td>2.2% (1)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

IVH: intraventricular hemorrhage; P: Fisher statistical exact.

### Table 7 - Refraction at month 9 post-treatment.

<table>
<thead>
<tr>
<th></th>
<th>IVH (n = 26)</th>
<th>Without IVH (n = 64)</th>
<th>Overall (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmetropes</td>
<td>15.4% (4)</td>
<td>45.3% (29)</td>
<td>36.7% (33)</td>
</tr>
<tr>
<td>Hypermetropes</td>
<td>38.5% (10)</td>
<td>35.9% (23)</td>
<td>36.7% (33)</td>
</tr>
<tr>
<td>Myopes</td>
<td>46.1% (12)</td>
<td>18.8% (12)</td>
<td>26.6% (24)</td>
</tr>
</tbody>
</table>

IVH: intraventricular hemorrhage; Pearson $\chi^2: p = 0.008$.

**Discussion**

In recent years, the number of premature births in our hospital has increased together with the number of ROP cases. The main cause is attributed to the increased use of in vitro fertilization techniques. Although it is estimated that in the next few years the number of severely immature births with survival possibilities will increase, to date this has not occurred because we observed that gestational age and weight at birth of treated babies has not changed significantly in the past 5 years.

The criteria followed for the screening were: gestational age at birth under or equal to 32 weeks and weight at birth under or equal to 1500 g and infants who, even though above these numbers, had an unstable course and required intervention according to pediatric criteria and we considered to be valid at the time. We are not aware of any premature baby with ROP that was unnoticed with the combination of the above criteria. We treated 4 infants having birth weights over 1500 g but with less than 32 weeks gestation, and 2 infants with 33 weeks gestation weighing under 1500 g. If said limits were reduced, these would have gone undiagnosed. In this sense, we agree with Hernández et al. who does not believe that it is possible to apply more restrictive criteria in his series without the risk of omitting two severe ROP cases.

In Table 2 it can be appreciated that the infants treated in these past 5 years were given oxygen therapy, with mechanical ventilation in 93.4% of cases and exhibiting a significant part of known risk factors for the appearance and development of ROP. In general, these are severe diseases that could require aggressive treatments, surgical interventions and could even be lethal. In fact, the mortality rate (7.3%) is higher than the overall Neonatology Unit rate.

The mean age at which the infants were treated was of 36 weeks. None of the infants were treated before 33 weeks. At the other end, one baby was treated at 44 weeks because his general condition (enterocolitis, sepsis, meningitis, etc.) did not allow it earlier.

The publication of ETROP produced changes in treatment indications. For this reason, in our series and after said publication there is a clear predominance of pre-threshold retinopathy with 84.35% of eyes. With these indications, we achieved 96.5% of good anatomic results. In Spain and following said criteria, González Viejo et al. obtained 96.2% of good results, with a mean weight at birth of 1015 g and a gestational age of 27.9 weeks, identical to ours. In turn, Serra published 88.2% of overall good anatomic results but including all the ROP forms. If only the pre-threshold ROP group is considered, which would be similar to our study, said percentage rises to 97.3%. In said study, the mean gestational age was of 27.2 weeks and the mean weight at birth of 899 g, something below our study. In ETROP, the high risk pre-threshold retinopathy group (which would be most similar to our own) had 9.1% of unfavorable structural results, although the infants included in that study had a weight at birth of 703 g and a gestational age of 25.3 weeks (which is below our study) and also included more eyes with retinopathy in area I (40%) that had worse prognosis and accordingly a comparison between both results would not be valid.

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of life. In this regard, the work of García Serrano et al.\textsuperscript{13} is noteworthy as he proved that a good weight gain in the first 4–6 weeks of life reduces the risk of plus disease in premature babies from multiple pregnancies.

A good visual response was obtained in 84.85% of treated eyes. If this result is compared to the results of Serra, they are closer to the pre-threshold group results (92%) than to the overall results (74.2%). This is logical because in our population there was a prevalence of pre-threshold infants.

The overall strabismus rate of our study (23.5%) is higher than that of Serra for the pre-threshold group (8%) or that of González Viejo (12.8%). We believe this is because infants with intraventricular hemorrhage (IVH) in which strabismus is more frequent account for almost a third of the treated population. If this group is excluded, the percentage goes down to 10.8%. The same principle is valid to explain the high frequency of nystagmus (10.3%).

We believe that said functional results, which are poor in comparison to anatomic results, are due to the significant weight of infants with neurological disease in our population, i.e. 32%. In 2002, Christianse et al.\textsuperscript{14} published that premature babies with IVH, in particular grade III and IV, have a higher probability of having strabismus and other ocular motility disorders as well as optic atrophy and ROP grade 3 or worse.

The form in which the visual function is assessed can lead to an over estimation of negative results because, in addition to the condition of the visual system overall, in the response of infants their attention plays a role and, in these cases, it is generally diminished.

In 1985 Whiting\textsuperscript{15} introduced the term cortical visual impairment (CVI) to describe the visual deficiency of infants caused by central nervous system damages that do not directly affect ocular structures. At present, prematurity is the main cause of CVI in developed countries. In contrast with adult cortical blindness, children who suffer brain damage when their brain is still growing may experience some degree of improvement over time. Accordingly, caution is required when reporting to parents the visual prognosis of these infants.

In what concerns refractive results, there are statistically significant differences between infants who had IVH and those who did not, with a higher frequency of myopia.

Finally, we believe that anatomic results can be improved and to this end it is necessary to avoid any delay in diagnostic and treatment. Functional results are more difficult to improve because, among other causes, they are due to neurological lesions the treatment of which does not directly depend on the ophthalmologist.

Carried out at the appropriate time, diode laser photocoagulation in retinopathy of prematurity has very good anatomic results (96.5% of success) and with very few complications. The visual dysfunction affecting infants with prematurity (15.15% of treated cases) is infrequently due to neurological disease and not only to the ROP sequel.

**Conflict of interests**

The authors have no conflict of interests to declare.