

## ARTIGO ORIGINAL

### INCIDENCE, TREATMENT AND OUTCOMES OF RETINOPATHY OF PREMATURITY AT HOSPITAL DE CLÍNICAS DE PORTO ALEGRE, BRAZIL

#### INCIDÊNCIA E RESULTADOS DO TRATAMENTO DA RETINOPATIA DA PREMATURIDADE NO HOSPITAL DE CLÍNICAS DE PORTO ALEGRE, BRASIL

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#### RESUMO

**Objetivos:** Avaliar a incidência geral da Retinopatia da Prematuridade (ROP) e a incidência da ROP em forma severa necessitando tratamento, assim como a evolução aos seis meses de idade nos nascidos pretermo admitidos na Unidade de Terapia Intensiva Neonatal do Hospital de Clínicas de Porto Alegre entre outubro de 2002 e outubro de 2006.

**Métodos:** Estudo de coorte, prospectivo, incluindo todos os pretermos com peso de nascimento  $\leq 1.500$  gramas ou com idade gestacional  $\leq 32$  semanas que sobreviveram até o momento do exame oftalmológico inicial. Todos foram examinados por oftalmoscopia binocular indireta entre a 4<sup>a</sup> e a 6<sup>a</sup> semana de vida com reavaliações periódicas de acordo com os achados baseados na Classificação Internacional da ROP.

**Resultados:** A ROP afetou 82 pacientes (25,5%). A doença severa necessitando tratamento ocorreu em 18 pacientes (5,6%). Dezessete pacientes realizaram tratamento de fotocoagulação por laser diodo. Três das crianças tratadas necessitaram uma segunda sessão de tratamento. Um dos pacientes re-tratados evoluiu com progressão necessitando cirurgia de retinopexia com banda de silicone epi-escleral. Um paciente perdeu a oportunidade do tratamento e desenvolveu cegueira total bilateral.

**Conclusões:** A incidência da doença bem como o percentual de crianças necessitando tratamento na instituição foi similar ao encontrado em outros centros internacionais. O tratamento foi eficiente para estabilizar e evitar a progressão para cegueira em 17 pacientes admitidos no hospital durante o período do estudo.

**Unitermos:** Prematuridade, retinopatia da prematuridade, terapia, complicações, prevenção, cegueira

#### ABSTRACT

**Objectives:** This paper aims to evaluate the overall incidence of retinopathy of prematurity (ROP), the rate of treatment in severe ROP, and the six-month outcomes in all preterm infants screened for ROP at Hospital de Clínicas de Porto Alegre, Brazil, between October 2002 and October 2006,

**Methods:** A prospective cohort study included all premature children born with birth weight  $\leq 1,500$  grams or a gestational age at birth  $\leq 32$  weeks. All patients were examined by indirect binocular ophthalmoscopy between the 4<sup>th</sup> and the 6<sup>th</sup> week of life. The examinations were repeated depending on the disease classification according the International Classification of ROP.

**Results:** Three hundred-twenty-two preterm infants were included in this study. ROP occurred in 82 infants (25.5%). Severe ROP occurred in 18 patients (5.6%). Seventeen of these were treated by diode laser photocoagulation. Three of the treated children needed a second laser session. One patient of the re-treated group needed scleral buckling surgery with an equatorial silicon band after progression for stage 4 of ROP. One patient missed the opportunity for laser and the disease progressed to stage 5 of ROP and blindness.

**Conclusions:** The incidence of retinopathy at our institution was similar to international results as well the as percentage of severe disease needing treatment. Laser photocoagulation was effective to stabilize the disease among 17 treated patients.

**Keywords:** Prematurity, retinopathy of prematurity, therapy, complications, blindness, prevention

#### INTRODUCTION

Retinopathy of prematurity (ROP) is a multifactorial disease affecting the development of the retinal vessels occurring, most frequently, in the smallest and sickest preterm babies. ROP is the leading cause of

childhood blindness and a worldwide disease under constant study due to the increasing survival of premature infants in many of the middle-income countries, among them Brazil (1-5).

In Brazil, Graziano et al, in 1997, analyzed the data of 102 prematures born with birth weight (BW) under

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1,500 grams and related 29.1% of ROP in any stage. The authors drove attention for the 78.5% prevalence of ROP among neonates born with BW under 1,000 grams and 72.7% of ROP among babies born under 30 weeks of gestational age (GA) (6).

In 2002, after the I Workshop for the Study of ROP, held in Rio de Janeiro, some decisions were taken in order to achieve a better understanding of the incidence of ROP in Brazil, and to reduce the incidence of blindness among surviving neonates by adequate prevention and early treatment whenever necessary. The *Hospital de Clínicas de Porto Alegre* (HCPA), after this meeting, implemented a screening program to detect the disease according to the Brazilian recommendations. The guidelines recommend binocular indirect ophthalmoscopy examination under dilation of pupils in all preterm infants with a BW equal to or less than 1,500 g or with a GA equal to or less than 32 weeks at birth, with initial ophthalmic examination between the 4<sup>th</sup> and the 6<sup>th</sup> week of life (7).

ROP is classified into stages 1–5 depending on severity. Stages 1 and 2 do not usually require treatment because the retinal changes regress spontaneously. In stage 3 occurs retinal neovascularization needing treatment. Stages 4 and 5 involve subtotal and total retinal detachment (8–10).

The number of seriously affected children in Brazil by the severe stages of ROP was estimated to be between 500 and 1,500 preterm babies *per year* from those babies born with BW  $\leq$ 1,500 grams and/or GA  $\leq$ 32 weeks) (11;12).

In the treatment, it is useful a laser or cryotherapy of the peripheral avascular retina to halt the progression of the affected retinal vascularization. Despite aggressive treatment, partial visual impairment or permanent blindness may result, in addition to other long-term eye problems like amblyopia, strabismus, high refractive errors, retinal detachment and glaucoma.

There is a very good anatomical prognosis after treatment, although many of the treated children achieve poor visual acuity by high refractive errors, presence of strabismus and partial retinal detachments secondary to the higher stages of ROP (13–16).

The objectives of this study were to evaluate the overall incidence of ROP, the rate of treatment by transpupillary diode laser in the patients with severe ROP and the main outcomes at six-month of age in infants screened for the disease in HCPA.

## METHODS

A prospective cohort study of all preterm neonates that met the recommended criteria for the Brazilian screening for ROP (BW  $\leq$ 1,500 g or GA  $\leq$ 32 weeks at birth) admitted to the HCPA from October 2002 to October 2006 was done. All were included, except for those infants that died during hospitalization before the moment of the initial ophthalmological examination. Those were excluded from this study.

The main clinical outcome was the occurrence of ROP in any of its evolutionary stages. Severe ROP was defined as ROP stage 3 or more.

The ophthalmological examination consisted of binocular indirect ophthalmoscopy with a 28 diopters Nikon® lens (Melville, NY, USA) and the lid speculum for newborns developed by Storz® (Alfonso Eye Speculum, Bausch & Lomb Inc., San Dimas, CA, USA), after the dilation of pupils with eye drops association of tropicamide 0.5% and phenylephrine 2.5%. Infants were first examined between the 4<sup>th</sup> and the 6<sup>th</sup> week of life with retinal mapping and staging of the disease according to the International Classification of ROP from 1984/1987 (17–19), and then followed depending on the severity of the disease until retinal vascularization was completed and to the end of the first year of life.

The treatment used the diode laser FTC 2500 Diode Laser®, 810 nm (Opto, São Carlos SP, Brazil) in all patients reaching severe ROP. Treatment was done with transpupillary photocoagulation with binocular indirect ophthalmoscopy under general anesthesia or sedation. Both eyes were treated at the same time. All of the ROP diagnosis and all treatments were performed by the same author JBFF.

All the exams were initially held at the Neonatal Intensive Care Unity and the follow-up examinations were conducted at the section of Ophthalmology.

A follow-up study was also performed and included only 91 prematures who presented for the follow-up appointment regularly until the 6 months of corrected age. Clinical six-month follow-up outcomes considered were: strabismus and the main refractive errors (myopia, hyperopia and astigmatism). All of the 91 patients had exams of the eye motility and alignment and cycloplegic refraction. Cycloplegic streak retinoscopy examination was carried out 30 minutes after the instillation of cyclopentolate 1%, phenylephrine 2.5% and tropicamide 0.5%, two drops each. Refraction was performed using handheld lenses in front of the awake infants.

The patients included in the follow-up study were allocated in 3 groups: Non-ROP patients; ROP patients and Severe ROP patients. Data about the incidence rates of the outcomes were described by number of patients and percents in each of the 3 groups, with the significance level of  $\alpha<0.05$ . The number of children included in the study was above the need for statistic confidence level of 95%. All data were processed in the software SPSS 13.0® (Statistical Package for Social Sciences). The study was approved by the ethics committee of the HCPA.

## RESULTS

Three hundred-twenty-two preterm infants were included in this study. Overall incidence of ROP in this cohort of patients was 25.5%. Severe ROP (stages 3 or more) occurred in 18 of the 322 babies screened for ROP (5.6%) (Table 1).

All cases with severe ROP were located in posterior Zone II, none in Zone I. Mean BW of the treated group was 918.6 grams and mean GA was 28.5 weeks. There was no statistical difference between gender, BW and GA among all of the cohort patients when compared with the patients with severe ROP (Table 2).

Transpupillary diode laser was used in the 17 treated cases with around 800 spots in each eye, without any complications of the treatment. Three patients needed a second laser treatment in both eyes, four weeks after the initial treatment. One patient of the re-treated group needed scleral buckling surgery with an equatorial silicon band after progression for stage 4 of ROP. One patient missed the opportunity to the laser treatment and the disease progressed to stage 5 of ROP without treatment. The anatomical outcome was good and a regression of the disease was achieved in all of the 17 treated neonates.

Ninety-one patients were studied for main outcomes at six-month of corrected age. From this group, 31 (34%) developed ROP at any stage and 9 patients (10%) needed laser treatment for severe ROP. At 6 months of corrected age, patients who developed ROP were significantly more myopic (10 patients, 31%) than those who did not (2 patients, 3.3%). Otherwise, non-ROP patients were significantly more hyperopic (51 patients, 85%) than the ROP group (21 patients, 67.7%). Astigmatism was present in 23 (74.1%) of the ROP patients and in 29 (48.3%) of the non-ROP infants. Among the patients who underwent laser therapy, 55.5% developed myopia. On the other hand, only 31% of the patients on ROP group without laser therapy developed myopia. Strabismus was detected in 4 patients on ROP group and in 3 patients on non-ROP group and in 2 babies treated by laser (Table 3).

## DISCUSSION

ROP was first reported in 1942 by Terry, who published a description of the histological findings of what would now be considered end-stage cicatricial disease (20;21). In its advanced forms, it can result in severe visual impairment or blindness, affecting the normal motor, language, conceptual, and social development of the child and having a high financial cost for the community (22).

Programs for the prevention of blindness from ROP were initiated in many countries, beginning in the 80's when the Cryotherapy for Retinopathy of Prematurity Cooperative Group (Cryo-ROP) demonstrated the first positive results from the treatment of this disease with cryotherapy (23-28).

In the management of ROP, several studies have demonstrated laser photocoagulation to be as effective as cryotherapy in reducing the incidence of unfavorable structural outcome, and nowadays most of the specialized centers in the treatment of ROP use the transpupillary photocoagulation by argon or diode laser applied by binocular indirect ophthalmoscopy as the best of the alternatives for treatment (29-31).

In the HCPA study here related, ROP at any stage affected 25.5% of the 322 neonates. Severe ROP needing treatment occurred in 18 of the screened babies (5.6%). All were treated with approximately 800 confluent laser spots at the peripheral avascular retina in each eye. The anatomical outcome was good in all neonates treated in spite of the 18.75% laser re-treatment required to stabilize the disease. The reason for this high re-treatment needing in patients with posterior Zone II disease could be the low number of laser spots applied to each eye. Bannach in 2000 and Rezai in 2005, published that the near confluent pattern of laser photocoagulation may reduce the rate of progression of threshold ROP in Zone II. The near confluent pattern with approximately 1,200 laser spots may also reduce the re-treatment rate of the disease, but larger studies are needed to confirm these findings (32;33).

McNamara et al. (34) analyzed in 1993 the complications of the laser photocoagulation treatment in ROP and showed mainly complications restricted to the anterior segment, as corneal edema, iris damage, lens damage and cataract formation. Most of the related complications at the anterior segment were observed after argon laser therapy and none with diode laser therapy. Retinal and choroidal hemorrhages, choroidal neovascularization, epi-retinal membrane formation and later retinal detachment were the main complications associated with the diode laser treatment for ROP. None of the 17 patients treated in the HCPA showed any of these complications.

In our study, all neonates were treated when ROP reached threshold disease, but recently, the results of a new multi centric and prospective clinical trial (The Early Treatment for ROP Cooperative Group) showed that treatments at the prethreshold disease significantly reduced unfavorable outcomes in both primary and secondary (structural) measures. These new results can induce the clinicians all over the world to treat the disease at the prethreshold moment (35).

Our study in the HCPA cohort suggests a higher risk for myopia (especially on ROP group that was submitted to laser treatment (55.5%). The association between myopia and ROP has been recognized for many years occurring mainly after cryotherapy, but also after the laser photocoagulation in spite of the laser producing less myopic shift (29).

Previous results from the multicenter study of Cryotherapy for ROP (Cryo-ROP) demonstrated that anisometropia, astigmatism, and presence of posterior pole residua from ROP are associated with higher incidences of myopia and high myopia ( $\geq 5.0$  Diopters). However, when results from treated versus control eyes were compared, there was little change in the distribution of the refractive error in treated or control eyes between 1 year and 10 years of age (36;37).

The etiology of myopia among prematures with ROP is still controversial needing further research into this subject to understand if the myopia is due to the disease or to the treatment (38).

## CONCLUSIONS

The transpupillary diode laser was effective to stop the natural progression of the disease in all of the 17 patients treated, in spite of one patient needing scleral buckling with an equatorial silicon band after progression for stage 4 of ROP. This study suggested a higher risk for myopia in the ROP group, but mainly in the Severe ROP group, where patients were submitted to retinal photocoagulation. These results are in agreement with other studies published in the literature.

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