·Clinical Research·

Retinopathy of prematurity in a tertiary center in south of Brazil

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Abstract

• AIM: To investigate the incidence of retinopathy of prematurity(ROP) in the southern Brazil, the rate of treatment and outcomes in all premature infants born at Hospital de Clinicas de Porto Alegre, Brazil, from October 2002 to October 2006.

• METHODS: A prospective cohort study was conducted on 323 premature children born at *Hospital de Clinicas de Porto Alegre*, Brazil, from October 2002 to October 2006 with birth weight equal to or less than 1 500g or a gestational age at birth of 32 weeks or less. All of the newborns were examined by indirect binocular ophthalmoscopy with the 28 diopters lens after pupil's dilation and a lid speculum after the sixth week of life with examinations repeated depending on the disease classification. The main clinical outcome was the occurrence of ROP at any stage.

• RESULTS: ROP occurred in 82 infants with an incidence rate of 25.7%. Threshold disease occurred in only 17 of the patients (5.3%), all of them had the disease affecting posterior Zone II needing laser treatment. None of the treated children had Zone I or aggressive posterior disease despite that three of the treated children needed a second laser session. One patient of the re-treated group needed scleral buckling with an equatorial silicon band after progression to stage 4 of ROP.

• CONCLUSION: The incidence of retinopathy and the threshold disease in this study was similar to the international results reported. This study showed a high survival rate (70.1%), high incidence of retinopathy, and high laser treatment necessity among newborns under 28 weeks of gestational age or under 1 000g of birth weight. This study drove attention about the no identification of any Zone I posterior disease in this cohort of patients.

• KEYWORDS: prematurity; blindness prevention; retinopathy of prematurity; ROP epidemiology; ROP incidence; ROP treatment

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INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness in all of the developed countries nowadays and also in many of the middle-income countries, like Brazil. ROP is a multifactorial disease affecting the development of the retinal vessels, occurring most frequently in the smallest and sickest infants. ROP is under constant study around the world due to the increasing survival of newborns of preterm delivery specially within the groups of greater risk for the appearance of this disease: very low birth weight (VLBW), comprised neonates born under 1 500g or under 32 weeks of gestational age (GA) at birth and extremely low birth weight (ELBW) including prematures born under 1 000g or under 28 weeks of GA at birth. In recent years, the survival rate in the ELBW patients increased from 8% to 35% in many of the middle-income countries [1-5].

The Brazilian recommendations for the ROP screening were established only after 2002 in a national meeting occurred in Rio de Janeiro. At that time some decisions were taken in order to achieve a better understanding of the incidence of ROP and to reduce the incidence of blindness by adequate prevention and early treatment whenever necessary. The *Hospital de Clinicas de Porto Alegre (HCPA)*, a universitary and tertiary care center hospital implemented after 2002 a screening program according to the standards defined for Brazil which recommended binocular indirect ophthalmos-

copy examination under dilation of pupils in all infants with a birth mass equal to or less than 1 500g or with a GA equal to or less than 32 weeks at birth[6,7].

The objectives of this study are to evaluate the incidence of ROP among VLBW and also among ELBW infants, the survival rate in these groups of patients, the rate of treatment and the main outcomes at HCPA between October 2002 and October 2006.

MATERIALS AND METHODS

Subjects The study was approved by the ethics committee of the HCPA and a prospective cohort study of all VLBW (defined as born under 1 500g or under 32 weeks of GA) infants born at the HCPA from October 2002 to October 2006 was done. All neonates that met the recommended criteria for the Brazilian screening for ROP were included, except for those infants that died during hospitalization before the 6th week of life, moment of the initial ophthalmological examination, that were excluded from this study.

Methods The incidence of ROP was evaluated among the ELBW infants (defined as group 1 and including all of newborns with BW under 1 000g at birth or GA less than 28 weeks at birth). The incidence of ROP was also evaluated among VLBW infants (group 2, defined over de extreme premature group but excluding in the group 2 all of the infants in the group 1). The main clinical outcome was the occurrence of ROP at any stage in both groups. The treatment was performed always in ROP 3 stage, threshold disease (defined as stage of ROP in which the chances of progression to retinal detachment are 50%, if left untreated)[7]. Main outcomes were described by mean and standard deviation with a confidence level of 95%. All data were processed in the software SPSS 13.0 (Statistical Package for Social Sciences).

All the exams were initially held at the Neonatal Intensive Care Unity (NICU) and the follow-up examinations were conducted in the section of Ophthalmology. The ophthalmological examination consisted of the external inspection of the eyeballs and 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 the pupils with association of the eye drops tropicamide 5g/L and phenylephrine 25g/L. Infants were first examined after the 6th week of life with retinal mapping and staging of the retinopathy according to the International Classification of Retinopathy of Prematurity from 1984/1987[8-10], and followed up depending on the severity of the disease until retinal vascularization was completed.

For the treatment the diode laser FTC 2500 Diode Laser, 810nm(Opto, São Carlos SP, Brazil) was used in all patients reaching threshold disease. Treatment was done with transpupillary photocoagulation with binocular indirect ophthalmoscopy under general anesthesia in surgical room or sedation in the NICU. Both eyes were treated in the same time.

A six-month follow-up study was performed; including the 91 prematures presented for the follow-up appointment. All the patients were examined for presumed visual acuity, exam of the eye motility and alignment, cycloplegic refraction, indirect ophthalmoscopy and retinal mapping. Cycloplegic streak retinoscopy and the fundus examination were carried out 30 minutes after the instillation of cyclopentolate 1g/L, phenilephrine 25g/L and tropicamide 5g/L, and two drops each. Refraction was performed using handheld lenses in front of the awaken infants.

RESULTS

Three hundred and twenty three patients were screened for ROP during the period and met the inclusion criteria for the study. Among them 113 were in the group 1. The survival rate among ELBW infants (group 1) reached 33.7% and 70.1% in the VLBW infants (group 2). ROP at any stage affected 42.5% of the ELBW infants and only 16.2% of the VLBW (OR 3.82; CI 2.19-6.68; P<0.0001). The ROP at any stage including the both groups in this institutional single-unit based approach occurred in 82 infants with an incidence rate of 25.7%. Mean BW in the group 1 was 910± 199g and in the group 2 was 1 349±193g. Mean GA in the group 1 was 28.1±2.0 weeks while in the group 2 was 31.4± 1.6 weeks (Table 1).

The stages of ROP among all the cohort is showed in Table 2 and the number of patients affected in different stages of ROP according to the BW is showed in Table 3.

Threshold disease occurred in only 17 of the 323 infants screened for ROP (5.0%). Among of them, 14 were in the ELBW group. The clinical characteristic of all treated patients was shown in the table 4. All threshold diseases were in posterior Zone II, none in Zone I. Mean BW of the treated group was 931±266g and mean GA was 28.4±2.4 weeks.

Transpupillary diode laser was used in all of the patients with confluent spots, around 800 in each eye, without any complications of the treatment. Three patients needed a

Table 1 Clinical characteristics of all the studied population

Clinical characteristics	Group 1 ELBW ≤1 000g	Group 2 VLBW >1 000g
n	113	210
Gender M (%)	51(45.1)	90 (42.9)
F (%)	62 54.9)	120 (57.1)
Birth mass(mean±sd,g)	910±199	1349±193
Gestational age (mean±sd,wk)	28.1±2.0	31±1.6

Table 2 Incidence of ROP among infants in HCPA between 2002 and 2006 *n* (%)

ROP	Group 1 ELBW ≤1 000g	Group 2 VLBW > 1 000g
Non-ROP	65 (57.5%)	176 (83.8%)
ROP	48 (42.5%)	34 (16.2%)
ROP 1	15 (13.3%)	20 (9.5%)
ROP 2	18 (15.9%)	10 (4.8%)
ROP 3 +	13 (11.5%)	4 (1.9%)
ROP 4	1 (0.9%)	0 (0.0%)
ROP 5	1 (0.9%)	0 (0.0%)
Total	113	210

Table 3 Number of affected patients in the worst stage of ROP by BW (*n*)

Birth mass(g)	Non-ROP	ROP 1	ROP 2	ROP 3	ROP 4	ROP 5
≤ 500	0	0	0	0	0	0
501-750	9	2	8	6	0	1
751- 1 000	33	10	8	6	1	0
1 001-1 500	159	22	12	5	0	0
> 1 500	40	1	0	0	0	0
Total of patients	241	35	28	17	1	1

Table 4 Main outcomes at six-month of age in 91 patients *n*(%)

Outcome	Non-ROP	ROP	Threshold ROP
Mean GA (range)/wk	29.4 (25-36)	30.8 (27-37)	30 (25-36)
Myopia	2 (3.3)	10 (31.0)	5 (55.5)
Hyperopia	51 (85)	21 (67.7)	4 (44.4)
Astigmatism	29 (48.3)	23 (74.1)	8 (88.8)
Strabismus	3 (5.0)	4 (12.0)	2 (22.2)

second laser treatment in both eyes, four weeks after the initial treatment. One patient of the re-treated group needed scleral buckling with an equatorial silicon band after progression for stage 4 of ROP. The anatomical outcome was good in all of the 17 neonates.

Ninety-one patients (182 eyes) were studied for main outcomes. From this group, 31 (34.0%) developed ROP at any stage and nine needed laser treatment for threshold disease. Mean GA for the non-ROP group was 29.4 weeks (range 25-36 weeks), compared to 30.8 weeks (range 27-37 weeks) for the ROP group. At six months of corrected age, patients who developed ROP were significantly more myopic (10 patients, 31.0%) than those who didn't (2 patients, 3.3%). Otherwise, non-ROP patients were significantly more hyperopic (51 patients, 85.0%) than the ROP group (21 patients, 67.7%). Astigmatism presented 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 31.0% 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 also in 2 babies treated by laser (Table 4) .

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 [11,12]. 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[13].

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 [7,14-18]. This large study set the incidence of ROP in some degree at 65.8% considering all patients and in 81.6% considering all children born with less than 1 000g[19].

Larsson *et al* [20] published the development of ROP in 25.5% of the 392 children prospectively studied in Stockholm, Sweden between 1998 and 2000 and also the appearance of stage 3 of ROP in 11.7%. Also in Europe, a retrospective study was published in 2002 about 194 children born prematurely with less than 1 500g or with less than 32 weeks of GA from 1992 to 2000. In this population, stages 1 and 2 occurred in 26.3% and only 2.5% of those examined needed cryotherapy[21].

At John Dempsey Hospital from the University of Connecticut School of Medicine, USA, between 1989 and 1997, the data of 950 newborns were evaluated retrospectively. The authors obtained 21.3% of ROP considering all stages and only 4.6% of the children examined reached stage 3 of ROP or more. This study also determined that none of the children born with more than 1 000g or with more than 28 weeks of GA developed stages of ROP that would need intervention by laser or by surgery[22].

In Brazil, the study by Graziano *et al* [23] published in 1997, analyzed retrospectively the data from 102 premature infants born with less than 1 500g from January 1992 to December 1993 and detected a percentage of 29.1% of ROP including all stages. This work stands out due to the very high prevalence of ROP (78.5%) in the group of patients with

BW less than 1 000g and 72.7% in infants born with GA of less than 30 weeks. The authors concluded that the children of lower BW or GA (below 1 000 g or below 28 weeks) have a greater risk of developing ROP in stage 3 or more.

Our findings confirmed the high incidence of ROP (42.5%) and threshold disease in the extremely premature group. In HCPA, the survival rate among ELBW infants was estimated over 33.7% and 70.1% in the VLBW. In the present study, ROP at any stage affected 42.5% of the ELBW and only 16.2% of the VLBW infants and threshold disease, needing laser treatment, occurred in 17 patients and, among them, 14 were included in the ELBW group.

Chen *et al*[24] in China (2006) reported that the mean GA of all the children reaching higher stages of ROP was 29.8 weeks (SD 1.9 weeks, range 26-34 weeks) and the mean BW was 1 432g (SD 319 g, range 760-2 500g) and that 31 babies of all 114 treated babies had BW more than 1 500g and the authors call attention to the fact that in China many bigger and more mature babies are developing severe and treatable ROP stages. These results differ in many aspects form the number related in our cohort of patients from Brazil.

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[25-27].

In our study, the 17 patients with threshold disease were considered for treatment with approximately 800 confluent laser spots at the peripheral avascular retina in each eye. The treatment regressed the disease in all treated patients despite of 17.6% laser re-treatment required. Some reasons for this high re-treatment level in patients with posterior Zone II threshold disease could be explained by 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 1200 laser spots may also reduce the re-treatment rate of the disease, but larger studies are needed to confirm these findings[28-29].

McNamara *et al*[30] 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, epiretinal membrane formation and later retinal detachment were the main complications associated with the diode laser treatment for ROP. None of the 16 patients treated in the HCPA showed any of these complications.

The objective of the systemic care of the newborns in the risk group for the development of ROP is to determine the adequate moment for treatment. In our study all neonates were treated in threshold disease once, classically, the threshold disease is considered the right moment to treat, 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[31].

Our study also suggests a higher risk for myopia (especially on ROP group that was submitted to retinal photocoagulation) and retinal changes among patients treated after developed ROP. 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 produces less myopic shift[25].

Theng *et al* [32] reported in 2000 that in Caucasian populations, premature infants with ROP have higher risks of developing refractive errors and strabismus. The risk of ROP was higher with lower BW and earlier GA. At 1-year follow-up, the rate of myopia was 33.3% in babies with ROP compared to 3.7% in babies with no ROP (P<0.001). The higher rates of myopia in babies with ROP remained with longer follow-up (33.3% and 25.0% in ROP group versus 3.4% and 3.8% in no ROP group, at 2 and 3 years respectively). These results look very similar with our observations in our follow-up cohort of 91 patients at HCPA, where at six-month of corrected age, patients who developed ROP were significantly more myopic (31.0%) than those who didn't (3.3%).

The results here presented in threshold disease are in agreement with other studies published in the literature in spite of the paper from Davitt *et al* [33] from the Early Treatment for ROP Cooperative Group that demonstrated

that the early treatment at a high-risk prethreshold did not raise the risk of developing myopia compared with conventional management. 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 high incidence of myopia (≥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[33-34].

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