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Research Article

Changing Paradigms in Retinopathy of Prematurity (ROP) in the Neonatal Intensive Care Unit of Hospital de Clínicas de Porto Alegre

Joao Borges Fortes Filho[1*], Gabriela Unchalo Eckert[1], Gustavo Afonso Santiago Gomes[2], Marcia Beatriz Tartarella[3]

[1]Ophthalmology Department, Medical School, Federal University of Rio Grande do Sul and Hospital de Clínicas de Porto Alegre, Porto Alegre RS, Brazil

[2]Ophthalmology Department Hospital de Clínicas de Porto Alegre, Porto Alegre RS, Brazil

[3]Ophthalmology Department, Centro Integrado de Oftalmologia Tartarella, São Paulo SP, Brazil

*Corresponding Author: Joao Borges Fortes Filho, Associate Professor of Ophthalmology, Ophthalmology Department, Medical School, Federal University of Rio Grande do Sul, Porto Alegre RS, Brazil.

Abstract

Objectives: This study aims to evaluate the incidence for ROP treatment among extremely low birth weight (ELBW) premature babies comparing two different periods in which an increase in the survival rates among ELBW occurred. **Methods:** A prospective cohort study was conducted from 2002 to 2024. Patients were included in 2 groups: Group 1 included neonates treated for severe ROP during the years 2002-2015 and group 2 included babies treated during the years 2016-2024. Variables were: birth weight (BW), gestational age (GA), post-conceptional age (PCA) at treatment. Outcomes were incidences of severe ROP in both groups, and regression of ROP after treatment during the entire observational period. Statistical comparisons between variables in both groups were performed. The significance level used was $P<0.5$. **Results:** The incidence of 12.8% of severe ROP needing treatment was reported during the entire period of the study. Group 1 included 23 patients and the incidence of ROP was 12.04%. Group 2 included 18 patients and the incidence of ROP was 14.06%, ($P = 0.198$). Mean BW and mean GA in group 1 were 808.0 ± 110.4g and 27.4 ± 1.9 weeks while in group 2 were 656.9 ± 111.6g and 25.1 ± 0,9 weeks, respectively. Post-conceptional age at treatment was 37.5 ± 1.4 weeks in group 1 and 36.2 ± 1.5 weeks in group 2 ($P<0,03$). According to the statistical analysis, both groups were different regarding the considered variables BW, GA, and PCA ($P<0.0001$, $P<0.0001$, and $P<0.03$), respectively. **Conclusions:** The higher survival rate, higher incidence of ROP and greater need of treatment in ELBW preterm babies indicate that these ELBW patients should receive special attention by ophthalmologists during the screening for ROP.

Abbreviations:

AntiVEGF: Anti Vascular Endothelial Growth Factors

BW: Birth Weight

ELBW: Extremely Low Birth Weight

GA: Gestational Age

HCPA: Hospital de Clínicas de Porto Alegre

NICU: Neonatal Intensive Care Unit

PCA: Post-Conceptional Age

ROP: Retinopathy of Prematurity

Introduction

Improvements in neonatal intensive care during the past decades resulted in a worldwide increase in the survival population of extremely low birth weight (ELBW) preterm babies [1-2]. These preterm neonates are highly vulnerable patients needing special attention in order to minimize avoidable consequences of the premature birth such as broncho-pulmonary dysplasia, intraventricular haemorrhage, and retinopathy of prematurity (ROP) which is an important cause of preventable childhood blindness among preterm infants. The incidence of blindness caused by ROP varies across countries, and is influenced by the quality of perinatal care and by the existence of screening programs for the early diagnosis of the disease [3].

This study aims to evaluate the incidence of ROP and need for treatment of ROP among ELBW premature babies in a level 3 University Hospital in Southern Brazil, in order to compare two different periods in which there was observed an increase in the survival rate among premature babies in our institution.

Population and methods

Setting: The study was carried out at the Neonatal Intensive Care Unit (NICU) of the Hospital de Clínicas de Porto Alegre (HCPA). This is a public level 3-university hospital in Porto Alegre, Brazil, an urban area with around 4.4 million of inhabitants. The NICU performs around of 130 admissions per year considering very low birth weight (VLBW) and ELBW preterm neonates. Routinely screening sessions to detect and to treat ROP are performed in around 93% of the admitted patients. The institutional survival rates for those inborn babies under BW ≤ 1,500g and for babies with BW ≤ 1,000 g was previously related at 71% and 41%, respectively [4-6]. The hospital is also a referral centre for patients of the Brazilian National System of Health for the Brazilian state of Rio Grande do Sul, the most Southern of the Brazilian states, which is highly considered for its standards of life quality.

Study design: An institutional and prospective cohort study was conducted comparing inborn ELBW preterm infants (defined as preterm infants born with BW ≤ 1,000g), that needed treatment for severe ROP between October 2002 and October 2024, comparing demographic characteristics of all treated patients in two different periods of time (2002-2015 and 2016-2024).

Population and methods: Staging of ROP was classified according to the International Classification of ROP from 1984/1987, as revisited in 2005 [7-9]. All patients were treated for ROP according to the Multicenter Cryotherapy for ROP Study (Cryo-ROP), Early Treatment for ROP Study (ET-ROP), and the Brazilian guidelines to detect and treat ROP [10-13]. All preterm infants with BW ≤ 1,000g who develop severe ROP needing treatment were included in the study, except for those that died during hospitalization before the first ophthalmological examination. There were no other exclusion criteria. Babies needing treatment were included in one of these two groups: Group 1 comprised ELBW preterm babies treated during the period from 2002 to 2015, and group 2 included the ELBW preterm babies treated during the period from 2016 to 2024. Initial ophthalmological examinations were performed between the 4th and 6th weeks of life and were repeated weekly according to the findings, and as outpatients for follow-up appointments until completed the first year of life.

Outcomes and variables: Considered variables were BW, gestational age at birth (GA), post-conception age (PCA) defined as GA + weeks of life, and type of treatment used as laser or anti vascular endothelial growth factor (antiVEGF) therapy. Main outcomes were the incidence of severe ROP during the entire period of the study and the regression of severe ROP after treatment during the entire observational period, and statistical comparisons between mean BW, mean GA and mean PCA at treatment in both groups.

Statistical methods and ethics: All of the continuous variables (BW, GA, and PCA) were tested for normal or abnormal distribution with the Shapiro-Wilk normality test. The BW variable followed a normal distribution; therefore, the homogeneity of variances was tested using Bartlett's test. Student's t-test for independent samples was used to compare the difference between groups. The GA and PCA variables did not follow a normal distribution; thus, the non-parametric Mann-Whitney test was used to compare the difference between groups. All statistical analyses were conducted using the R Core Team Software® (The R Project for Statistical Computing 2024). Data were described by mean, standard deviation, and range. The significance level used was $P < 0.5$.

The study protocol was approved by the Research Ethics Committee of HCPA and it is conformed to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh, 2000).

Results

A total of 319 ELBW preterm infants were screened for ROP during the entire period of the study comprised from 2002 to 2024. In this same period, a total of 41 ELBW preterm infants develop severe ROP needing treatment and were included in the study. The incidence of 12.8% of severe ROP needing treatment among ELBW was reported during the entire period of the study.

Group 1 (period 2002-2015) included 23 treated patients (among 191 screened babies) and the incidence of ROP in this period was 12.04%. Group 2 (period 2016-2024) included 18 treated patients (among 128 screened babies) and the incidence of ROP in this period was 14,06%. The difference between the incidence of patients requiring treatment in both groups was not significant ($P = 0.1982$).

Mean BW and mean GA for the entire cohort was 741.7 ± 133.3g (range 505-990g) and 26.4 ± 1.9 weeks (range 24-31 weeks), respectively. Mean BW and mean GA in group 1 were 808.0 ± 110.4g and 27.4 ± 1.9 weeks while in group 2 were 656.9 ± 111.6g and 25.1 ± 0,9 weeks, respectively. Post-conceptional age at treatment was 37.5 ± 1.4 weeks in group 1 and 36.2 ± 1.5 weeks in group 2 ($P < 0,03$). According to the complete statistical analysis, both groups of treated patients were different regarding the 3 considered variables BW, GA, and PCA ($P < 0.0001$, $P < 0.0001$, and $P < 0.03$), respectively.

Transpupillary diode laser was used as mono-therapy in all 23 patients in group 1 while laser mono-therapy was used in 10 patients in group 2. AntiVEGF as mono therapy was used in 6 patients and, as a combined-therapy (antiVEGF plus laser), in 2 patients in group 2. All of the 41 ELBW treated during the entire observational period, from 2002 to 2024, achieved regression of ROP (Tables 1 and 2).

GROUP 1							
Case	GA	BW	ROP STAGE	ZONE	TREATMENT	PCA	OUTCOMES
1	26	710	ROP 3+ Threshold	Zone II	Laser	36	Regression
2	31	780	ROP 3+ Threshold	Zone II	Laser	40	Regression
3	27	635	ROP 3+ Threshold	Zone II	Laser	36	Regression
4	30	935	ROP 3+ Threshold	Zone II	Laser	37	Regression
5	26	625	ROP 3+ Threshold	Zone II	Laser	36	Regression
6	25	620	ROP 3+ Threshold	Zone II	Laser	36	Regression
7	29	990	ROP 3+ Threshold	Zone II	Laser	39	Regression
8	31	900	ROP 3+ Threshold	Zone II	Laser	40	Regression
9	26	700	ROP 3+ Threshold	Zone II	Laser	36	Regression
10	30	870	ROP 3+ Threshold	Zone II	Laser	40	Regression
11	25	755	ROP 3+ Threshold	Zone II	Laser	36	Regression
12	28	750	ROP 3+ Threshold	Zone II	Laser	38	Regression
13	28	850	ROP 3+ Threshold	Zone II	Laser	37	Regression
14	26	890	ROP 3+ Threshold	Zone II	Laser	37	Regression
15	28	730	ROP 3+ Threshold	Zone II	Laser	37	Regression
16	27	920	ROP 3+ Threshold	Zone II	Laser	37	Regression
17	26	910	ROP 3+ Threshold	Zone II	Laser	36	Regression
18	26	885	ROP 3+ Threshold	Zone II	Laser	38	Regression
19	26	920	ROP 3+ Threshold	Zone II	Laser	37	Regression
20	28	770	ROP 3+ Threshold	Zone II	Laser	38	Regression
21	25	710	ROP 3+ Threshold	Zone II	Laser	38	Regression
22	26	810	ROP 3+ Threshold	Zone II	Laser	39	Regression
23	30	920	ROP 3+ Threshold	Zone II	Laser	38	Regression

Number of screened patients = 191
Incidence of ROP = 12.04%
GA: gestational age; BW: birth weight; PCA: postconceptional age at treatment
Group 1 mean GA: 27.4 weeks (SD: 1.9); range: 25-31 weeks
Group 1 mean BW: 808g (SD: 110.4); range: 620-990g
Group 1 mean PCA: 37.5 weeks (SD: 1.4); range: 36-40 week

Table 1: demographic characteristics of all treated patients during 2002-2015.

GROUP 2							
Case	GA	BW	ROP STAGE	ZONE	TREATMENT	PCA	OUTCOMES
1	26	505	ROP 3+ Threshold	Zone II	Laser	37	Regression
2	25	570	ROP 3+ Threshold	Zone II	Laser	37	Regression
3	26	600	ROP 3+ Threshold	Zone II	Laser	37	Regression
4	26	890	ROP 3+ Threshold	Zone II	Laser	37	Regression

5	26	820	ROP 3+ Threshold	Zone II	Laser	37	Regression
6	24	675	ROP 3+ Threshold	Zone II	Laser	37	Regression
7	24	650	ROP 3+ Threshold	Zone II	Laser	37	Regression
8	26	605	Type 1 ROP	Zone I	Laser	37	Regression
9	24	650	AP-ROP	Zone I	AntiVEGF + Laser	36	Regression
10	26	670	AP-ROP	Zone II	AntiVEGF + Laser	36	Regression
11	25	785	ROP 3+ Threshold	Zone II	Laser	37	Regression
12	26	790	ROP 3+ Threshold	Zone II	Laser	37	Regression
13	25	500	AP-ROP	Zone I	AntiVEGF	36	Regression
14	24	695	ROP 3+ Threshold	Zone II	AntiVEGF	33	Regression
15	24	690	ROP 3+ Threshold	Zone II	AntiVEGF	37	Regression
16	26	570	ROP 3+ Threshold	Zone II	AntiVEGF	37	Regression
17	25	500	ROP 3+ Threshold	Zone II	AntiVEGF	33	Regression
18	24	660	ROP 3+ Threshold	Zone II	AntiVEGF	33	Regression

Number of screened patients = 128

Incidence of ROP = 14.06%

GA: gestational age; BW: birth weight; PCA: postconceptional age at treatment; AP-ROP: aggressive posterior ROP

Group 2 mean GA: 25.1 weeks (SD: 0.9); range: 24-26 weeks

Group 2 mean BW: 656.9g (SD: 111.6); range: 500-890g

Group 2 mean PCA: 36.2 weeks (SD: 1.5); range: 33-37 weeks

Table 2: demographic characteristics of all treated patients during 2016 – 2024.

Discussion

Over the last 10 years, epidemiological studies showed higher incidence of severe ROP and higher need for treatment among ELBW babies. These patients have been showing decreasing mortality rate in the last years in developed countries, as well as in some developing countries like Brazil [1,5,6].

Brazilian guidelines state treatable ROP when disease reach ROP zone I, any stage with plus disease; ROP in zone I, stage 3 with no-plus; or ROP in zone II, stages 2 or 3 with plus disease or at least, at threshold ROP [13]. In more recent years the indications for ROP treatment in most of the developed countries are at type 1 ROP, defined according to the ET-ROP, from 2003, but in many of the middle-income countries, and especially those in South America, the treatment continues to be performed at threshold ROP, as defined according to the Cryo-ROP [10].

In this way, all of the patients of our study were treated at threshold ROP and the assessments were repeated periodically, according to the Brazilian guidelines [13].

In this study it was observed that both groups were different in terms of BW and GA. Babies in group 2 had statically lower mean BW and lower mean GA when compared to babies in group 1, meaning that in the period from 2016-2024 the survived treated ELBW preterm babies were smaller and more immature babies when compared with the survived treated ELBW infants from the period between years 2002 to 2015. This situation could have been influenced by better prenatal and neonatal care during the last decades. Some centres show that survival rates among 27-28 weeks preterm babies is up to 90% and among 32 weeks or more preterm infants is above 95% in more recent years, although this number vary widely across centres [1,2]. Among better prenatal care are administration of corticoids and programs to develop strategies to reduce the incidence of preterm labour. Advances in neonatal care include modern incubators with better control thermal environment, development of better mechanical ventilators, including the high frequency ones, the early use of nasal CPAP (continuous positive airway pressure) immediately or shortly after birth, use of drugs like surfactant, erythropoietin and indomethacin, besides sophisticated ultrasonography and X-ray devices to identify associated morbidities in this highly susceptible population of patients [14].

Nowadays, especially in more developed countries, the incidence and severity of ROP are described as having an inverse relationship

to BW and GA, with few cases of severe ROP being diagnosed in babies with BW higher than 1,500g or older than 32 weeks of GA [5], but over the last 10 years, epidemiological studies showed higher incidence and higher need for treatment among ELBW babies related to the decreasing mortality rate in the last years [1-6].

From 2002 to 2024, our institutional team in HCPA improved neonatal intensive care with the best possible technologies considering:

1) Optimization of oxygen therapy since birth at delivery room with the use of pulse oximetry in all VLBW and ELBW preterm babies with recommended saturation pressure between 88 and 94%.

2) Keeping strict control over the main risk factors for severe ROP.

3) Adopting the use of total parenteral nutrition optimization for babies with BW<1,250g.

4) Adopting an institutional ophthalmological screening program to detect and to treat ROP in the best moment.

5) Recommending the use of the ROPScore as a tool in order to help ophthalmologists to minimize unnecessary ophthalmological examinations in these vulnerable preterm infants once repeated eye examinations can cause stress and physical debilitation in the preterm babies.

6) Performing treatment for severe ROP always around the 37th week of PCA, as recommended since the Cryo-ROP study [10].

ROPScore, as previously reported [15], is a score system which allow for a reduction in the number of ophthalmological examinations performed in the same patient during the screening for ROP. ROPScore is a robust predictor of ROP onset including risk factors for ROP that are easy to record. It is more accurate than BW and GA to predict the occurrence of ROP in preterm infants and reduce the excessive number of eye examinations performed in VLBW and in ELBW preterm infants in order to detect severe cases of ROP needing treatment. ROPScore is simple enough to be routinely used by ophthalmologists or by the NICU staff during screening examination to detect ROP [15].

At HCPA, to accomplish tighter control of oxygen therapy, strict guidelines are applied. All neonates in critical condition are permanently controlled by the use of pulse oximetry with a recommended oxygen saturation pressure between 88 and 94%, when babies are in oxygen therapy [16]. This kind of postnatal care is of crucial importance to avoid fluctuations during oxygen therapy to minimize the risk for severe ROP, as were achieved in our institution during the period from 2008 to 2015, when our incidence of treatable ROP dropped to 0% during 7 consecutive years among ELBW, but after 2016 the incidence of treatment among ELBW preterm infants raised again in the institution despite all of the staff care in the oxygen therapy.

Question is why this? After observing an increase in the need for treatments that occurred after 2015, we arbitrarily decided to divide the entire cohort of treated ELBW during the entire observational period of the study (2002-2024) into 2 groups: group 1 referring to the period between 2002 and 2015 and group 2 between 2016 and 2024, and it was hypothesised that we have now a smaller and more immature group of babies developing severe ROP despite all of the recent improvements of the intensive care achieved in our institution in order to minimize ROP. In one previous article we published about the influence of GA on the dynamic behaviour of the risk factors associated with ROP [17] where smaller preterm babies are surviving longer and very immature babies will develop ROP *per se* meaning that just for the immaturity itself the smaller babies have higher chance to develop severe ROP, despite the optimization in all of the clinical parameters in the ELBW preterm care, as well as in the nursery neonatal practices. In our institution, the NICU staff is regularly trained on the relationship between hyperoxemia and ROP. This training is helpful because it is possible to control and to prevent the occurrence of severe ROP in most cases only by carefully monitoring hyperoxia and avoiding fluctuations.

In this study it was clinically observed and statistically analysed that in the period from 2016-2024 the survived and treated for ROP ELBW preterm babies were smaller and more immature babies when compared with the survived and treated ELBW infants from the period between years 2002 to 2015. This situation can explain the recent increase for ROP treatment among smaller and more immature ELBW preterm infants who develop severe ROP despite all of the neonatal improvements used in our institution.

Our results drove attention that ROP in Zone 1 or Aggressive Posterior ROP (AP-ROP) was detected in only 3 patients during the entire observational period and, in our opinion, all of the institutional improvements in the neonatal practices contributed for this.

Finally, all of the 41 ELBW treated during the entire observational period, from 2002 to 2024, achieved regression of ROP avoiding blindness in this cohort of patients.

Conclusions

This study was carried out during the past 22 years, and many practices of neonatal care may have improved worldwide, or even achieved local improvement such as better control over the oxygen use since birth, better ventilation techniques, widespread use of pulse oximetry avoiding fluctuations during oxygen therapy, Improvements were also obtained in parenteral feeding for ELBW and routinely less use of vascular endothelial growth factor drugs, as erythropoietin, for example [4].

The higher survival rate, higher incidence of ROP and greater need of treatment in ELBW preterm babies indicate that this group of patients (born with BW under 1,000g) should receive special attention by ophthalmologists during the screening for ROP.

Is important to note that this study was conducted in only one institution, where guidelines for treating high risk premature infants are applied without exceptions. This is not a population-

based study and it was not conducted in a multicentre way, so our observations should only be applied to patients who are cared in the same conditions as the ones at HCPA.

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Contribution of the Authors

All the authors participated in the writing of the manuscript. All authors have read and approved the final version of the manuscript.

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