Postconceptional age at the treatment of retinopathy of prematurity in inborn and referred preterm infants from the same institution

Idade pós-concepção no tratamento da retinopatia da prematuridade em pré-termos nascidos e em transferidos para o tratamento em uma mesma instituição

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ABSTRACT

Purpose: The outcomes of the treatment of retinopathy of prematurity (ROP) seem to be better in inborn patients than in those patients who were referred for ROP treatment. This study aims to investigate the timing of treatment and the outcomes in inborn patients and in patients referred for treatment to the Hospital de Clínicas de Porto Alegre, Brazil.

Methods: An institutional prospective cohort study was conducted from 2002 to 2010 and included in group 1 all inborn preterm neonates treated for retinopathy of prematurity and in group 2 all babies referred for treatment to the same institution. All of the included patients presented birth weight (BW) ≤1,500 g and/or gestational age (GA) ≤32 weeks. Main outcomes were postconceptional age at the treatment and one year follow-up outcomes in both groups. The considered variables were: BW, GA, stage and location of retinopathy of prematurity at treatment.

Results: Group 1 comprised 24 inborn patients. Mean BW and GA at birth were 918 ± 232 g and 28.2 ± 2.1 weeks, respectively, and median post-conceptional postconceptional age at treatment was 37 weeks. Group 2 comprised 14 infants transferred for treatment. Mean BW and GA at birth were 885 ± 188 g and 28.2 ± 2.4 weeks, respectively, and median postconceptional age at treatment was 39 weeks. Mean BW and GA were similar in both groups (P=0.654 and P=0.949, respectively), but the difference among the postconceptional age was significant (P=0.029).

Conclusions: Inborn patients were treated for retinopathy of prematurity during the 37th week of postconceptional age while transferred patients were treated, usually, after the 39th week postconceptional age. The worst outcomes observed among referred patients could be partially explained by the delayed time for treatment.

Keywords: Infant, very low birth weight; Retinopathy of prematurity/therapy; Gestational age; Hospitals, public; Risk factors; Survival rates

RESUMO

Objetivos: *Os resultados do tratamento da retinopatia da prematuridade (ROP) parecem ser melhores em pacientes nascidos na mesma instituição onde o tratamento foi praticado do que naqueles pacientes transferidos para o tratamento em centros de referência. Este estudo tem como objetivos investigar o momento do tratamento e seus resultados em pacientes nascidos e em pacientes transferidos para o tratamento em uma mesma instituição.*

Métodos: *Estudo de coorte institucional e prospectivo conduzido de 2002 a 2010 e incluiu no grupo 1 todos os prematuros tratados para a retinopatia da prematuridade nascidos na instituição e no grupo 2 todos os prematuros tratados para a retinopatia da prematuridade transferidos para o tratamento. Todos os pacientes incluídos tinham peso de nascimento (PN) ≤1.500 gramas e/ou idade gestacional (IG) ≤32 semanas. As principais consideradas foram a idade pós-concepção (IPC) por ocasião do tratamento e os resultados do tratamento ao final do 1º ano de vida dos pacientes nos 2 grupos. As variáveis consideradas foram: peso de nascimento, idade gestacional, estadiamento e localização da retinopatia da prematuridade por ocasião do tratamento.*

Resultados: *O grupo 1 incluiu 24 prematuros nascidos na instituição. As médias do PN e da IG foram 918 ± 232 gramas e 28,2 ± 2,1 semanas, respectivamente. A mediana da idade pós-concepção ao tratamento foi de 37 semanas. O grupo 2 incluiu 14 pacientes transferidos para o tratamento. As médias do PN e da IG foram 885 ± 188 gramas e 28,2 ± 2,4 semanas, respectivamente. A mediana da idade pós-concepção ao tratamento foi de 39 semanas. As médias dp PN e da IG eram similares nos dois grupos (P=0,654 e P=0,949, respectivamente), mas a diferença entre a idade pós-concepção ao tratamento foi significativa entre os 2 grupos (P=0,029).*

Conclusões: *Os pacientes nascidos na instituição foram tratados para a retinopatia da prematuridade durante a 37ª semana de idade pós-concepção enquanto os pacientes transferidos foram tratados após a 39ª semanas de idade pós-concepção em média. Os piores resultados do tratamento assim como do seguimento de um ano observados entre os pacientes do grupo 2 podem ser explicados, em parte, pelo tempo maior decorrido para o tratamento da retinopatia da prematuridade.*

Descritores: *Recém-nascido de muito baixo peso; Retinopatia da prematuridade/terapia; Idade gestacional; Hospitais públicos; Fatores de risco; Taxa de sobrevida*

INTRODUCTION

Retinopathy of prematurity (ROP) remains one of the leading causes of preventable childhood blindness especially in middle-income countries, where improvements in the perinatal care increased survival rates among very low birth weight (VLBW) preterm neonates[1]. Despite the availability of ROP treatment by cryotherapy[2], laser photocoagulation[3] or surgical procedures as pars plicata vitrectomy[4] and, recently, by the use of intravitreous anti-VEGF therapy[5],

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the outcomes for those treated patients remains not as good as desirable[6,7].

In more recent years, the indications for ROP treatment in most of the developed countries are high risk type 1 ROP, defined according to the Early Treatment for ROP Study (ET-ROP), from 2001[8], but in many of the middle-income countries, and especially those in South America, the treatments continue to be performed at threshold ROP, as defined according to the Multicenter Cryotherapy for ROP Study (Cryo ROP), from 1988[2].

We hypothesized that inborn patients were treated sooner than the transferred patients and this factor could have some negative influence at the outcomes for the transferred patients. Our study aims to investigate on this very practical subject for ophthalmologists in charge of performing screening and treatment for ROP.

METHODS

Study design

An institutional and prospective cohort study was conducted comparing preterm infants with birth weight (BW) ≤1,500 g and/or gestational age (GA) ≤32 weeks inborn at Hospital de Clínicas de Porto Alegre (HCPA) that needed treatment for ROP with patients transferred to the same institution for treatment of ROP. The study was carried out between October, 2002 and May, 2010.

Setting

The study was conducted at the neonatal intensive care unit (NICU) of the HCPA in Porto Alegre, Brazil. This is a public level 3-university hospital in an urban area with around 3 millions of inhabitants. The NICU has 20 fully equipped intensive care beds and performs around 130 admissions per year considering only VLBW preterm neonates. Routinely screening sessions to detect and treat ROP are performed in more than 95% of the admitted VLBW. The institutional survival rates for inborn babies under BW≤1,500 g and BW ≤1,000 g were previously related as 71% and 41%, respectively[9].

Population and methods

The patients were included in one of these groups: group 1 comprised all inborn preterm neonates with BW ≤1,500 g and/or gestational age GA ≤32 weeks treated for ROP and group 2 comprised babies with the same BW's and GA's characteristics but referred for treatment to the institution (this BW and GA characteristics are according to the statements of the Brazilian screening criteria to detect and treat ROP, as above mentioned)[10].

All included patients were treated for ROP according to the Cryo ROP[2], and to the Brazilian guidelines to detect and treat ROP[10].

Despite the indications for the treatment of ROP have been changed from threshold ROP (as defined by the Cryo-ROP) to a high risk type 1 ROP (as defined by the ET-ROP)[8], all patients of our study were treated at threshold ROP. The assessments were repeated periodically, according to the Brazilian guidelines for examining and treating ROP[10] which recommend screening for all babies with BW ≤1,500 g and/or GAd≤32 weeks and for those babies with risk factors as respiratory distress syndrome, sepsis, intraventricular hemorrhage, babies who needed blood transfusions, and for those being born from multiple gestations. The initial ophthalmological examination was performed between the 4th and 6th weeks of life and were repeated weekly or more frequently according to the findings until full vascularization of the peripheral retina was observed or until 45 weeks of postconceptional age (PCA). The Brazilian guidelines state treatable ROP in 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[10,11].

ROP was classified according to the International Classification of Retinopathy of Prematurity (stages 1 to 5)[12,13]. All of the included patients received outpatient follow-up appointments until completed the first year of life.

All of the patients in both groups were treated by the same ophthalmologist and vitreous-retinal specialist (JBFF). The one year follow-up examinations were performed by the pediatric ophthalmologists (GUE, FBV, PGBS).

The study was conducted from 2002 to 2010 and there were no exclusion criteria.

Outcomes and variables

Main outcomes were PCA in weeks at treatment (defined as GA + weeks of life) and the treatment outcomes. The ophthalmological examination at the first year of life included search for abnormal visual behavior, strabismus and significant ametropia. We attempted to evaluate binocular visual acuity (VA) in most of the children using Teller's test or Kay's pictures. Refraction was calculated by light retinoscopy under cycloplegia after 30 minutes of two drops of 1% cyclopentolate in both groups of patients with prescription of corrected lenses if there were myopia, hyperopia or astigmatism of more than 3 dioptries. The considered variables were: BW, GA, stage and location of ROP at treatment, and the one-year refractive status in both groups of patients.

Statistical methods and ethics

All statistical analyses were conducted using the SSPS software (SPSS® 16.0 for Windows®; SPSS Inc., Chicago, IL, USA). Independent sample Student's-t test was used to compare both groups of treated patients. Effect size and 95% confidence interval were calculated for PCA.

The study protocol was approved by the Research Ethics Committee of HCPA (document 04-207) and it is conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh, 2000).

RESULTS

Group 1 comprised 24 inborn patients. Mean BW and GA were 918 ± 232 g and 28 ± 2.0 weeks, respectively. Median PCA at treatment was 37 weeks. Group 2 comprised 14 infants referred for ROP treatment. Mean BW and GA were 885 ± 188 g and 28 ± 2.4 weeks, respectively. Median PCA at treatment was 39 weeks. Mean BW and GA were similar in both groups (P=0.654 and P=0.949, respectively), but the difference among PCA at treatment in the both groups was significant (P=0.029). The complete data regarding both groups are shown in tables 1 and 2.

At the one-year follow-up examination, a higher occurrence of strabismus was observed in the group 2 in a total of 4 patients with esotropia (ET) and one patient with exotropia (XT), while in the group 1 only one patient developed XT. Myopia ≥3.00 dioptries was observed in 7 patients in the group 1 and in 6 patients in the group 2. The most complete refractive and anatomical one-year outcomes for the two groups are shown in tables 1 and 2.

DISCUSSION

The incidences of any stage of ROP and severe ROP that required treatment in inborn patients in our institution were previously related as 29.9% and 7.4%, respectively, which is a very low percentage, even for countries with established standards of excellence in perinatal care[14].

Mean BW and GA for the inborn at HCPA treated for ROP in our study were 918 ± 232 g and 28 ± 2.0 weeks, respectively. These data show a lower BW and GA cohort of treated patients when compared to a similar data (1,369 ± 184 g and 30 ± 1.8 weeks) from a recent published article from Hanoi, Vietnam, a country in transitional economy, like Brazil[15]. Lower GA and BW have been implicated in the occurrence of ROP in most studies and both are considered the most important risk factors for severe ROP that require treatment in different populations and in different countries[16,17].

Our study did not show statistical differences regarding BW and GA in both groups (group 1: 918 g and 28 weeks versus group 2: 885 g and 28 weeks, P=0.654 and P=0.949, respectively) but it disclosed that inborn patients were treated for ROP during the 37th week of PCA while referred patients were treated, usually, after the 39th week of PCA, being this difference significant (P=0.029).

Table 1. HCPA inborn patients treated for ROP

Case	GA	BW	Stage of ROP at treatment	ROP zone	GA at treatment	Treatment	Anatomical results	Refractive outcomes
1	25	620	3 +	II	36	Laser 1 x OU	Regression	-6.00/-6.00
2	25	755	3 +	II	36	Laser 1 x OU	Regression	-6.00/-5.00
3	26	625	3 +	II	36	Laser 2 x OU	Regression	-5.00/-2.00
4	26	700	3 +	II	36	Laser 1 x OU	Regression	+2.00/+2.00
5	26	710	3 +	II	36	Laser 1 x OU	Regression	+2.00/+1.00
6	26	890	3 +	II	37	Laser 1 x OU	Regression	-0.50 -1.50 (180) OU
7	26	1,080	3 +	II	37	Laser 1 x OU	Regression	+3.00/+3.00
8	27	635	3 +	II	36	Laser 1 x OU	Regression	-3.00/-4.00
9	27	920	3 +	II	34	Laser 1 x OU	Regression	Deceased
10	27	1,055	3 +	II	39	Laser 1 x OU	Regression	+2.00/+2.00
11	28	730	3 +	II	41	Laser 1 x OU	Regression	+2.00/+1.00
12	28	750	3 +	II	38	Laser 1 x OU	Regression	+3.50 -1.50 (180) OU
13	28	850	3 +	II	37	Laser 1 x OU	Regression	-1.00 -3.50 (180) -1.00 -4.00 (180)
14	28	1,260	3 +	II	37	Laser 1 x OU	Regression	-2.50/3.00
15	29	990	3 +	II	39	Laser 1 x OU	Regression	-1.50 -3.50 (180) -2.00 -3.50 (180)
16	29	1,020	3 +	II	41	Laser 1 x OU	Regression	+3.00 -2.00 (180) OU
17	30	870	3 +	II	40	Laser 1 x OU	Regression	-3.00 -1.00 (180) OU
18	30	920	3 +	II	38	Laser 2 x OU	Progression to ROP 4A	-6.00 OU
19	30	935	3 +	II	37	Laser 1 x OU	Regression	-6.00 OU
20	30	1,500	3 +	II	40	Laser 1 x OU	Regression	-8.00 fixing 1 eye
21	31	780	3 +	II	40	Laser 2 x OU	Regression	+0.50 OU
22	31	900	3 +	II	40	Laser 1 x OU	Regression	+2.00 OU
23	31	1,230	3 +	II	40	Laser 1 x OU	Regression	-2.00 -3.50 (180) OU
24	32	1,315	3 +	II	41	Laser 1 x OU	Regression	-1.00/-1.00
Mean	**28.2**	**918.3**			**38.0**			
Median	**28.0**	**895.0**			**37.0**			
SD	**2.1**	**231.7**			**2.0**	3 patients needed 2x laser treatment		
Min	**25**	**620**			**34**			
Max	**32**	**1,500**			**41**			

HCPA= Hospital de Clínicas de Porto Alegre; ROP= retinopathy of prematurity; BW= birth weight; GA= gestational age; += plus disease; SD= standard deviation; OU= both eyes

Table 2. Patients referred for ROP treatment

Case	GA	BW	Stage of ROP at treatment	ROP zone	GA at treatment	Treatment	Anatomical results	Refractive outcomes
1	25	830	3 +	II	42	Laser 2 x SB OU	Progression to ROP 4B OU	NDA
2	26	640	3 +	II	38	Laser 1 x OU	Regression	-3.50 -2.00 (180) OU
3	26	705	3 +	II	38	Laser 1 x OU	Regression	-2.00 (90) OU
4	26	840	3 +	II	38	Laser 1 x OU	Regression	-3.50 -2.00 (180) OU
5	26	865	3 +	II	40	Laser 1 x OU	Progression to ROP 4A OS	-2.50 OS fixing 1 eye
6	26	905	3 +	I- APROP	37	Laser 1x OU + Avastin 1x OS	Regression	-5.00/-5.00 fixing 1 eye
7	28	660	3 +	II	40	Laser 1 x OU	Regression	-4.00/-3.00
8	29	990	3 +	II	39	laser 1 x OU	Regression	-2.00 (180) OU fixing 1 eye
9	29	1,150	3 +	II	39	Laser 2x + SB OU	Progression to ROP 4A OU	-4.50 -3.00 (180) OS fixing 1 eye
10	30	725	4A	II	39	Laser 1 x OU	Progression toROP 4B OS	-1.50/-2.50 fixing 1 eye
11	30	865	3 +	II	39	Laser 1 x OU	Regression	+1.50 -1.00 (180) OU
12	30	890	3 +	II	39	Laser 1 x OU	Regression	-3.00/-4.00
13	32	1,015	3 +	II	42	Laser 1 x OU	Regression	NDA
14	32	1,315	3 +	II	40	Laser 1 x OU	Regression	-5.00/-5.00
Mean	**28.2**	**885.4**			**39.3**			
Median	**28.0**	**865.0**			**39.0**			
SD	**2.4**	**187.7**			**1.4**	2 patients needed 2x laser treatment + SB		
Min	**25**	**640**			**37**	1 patient needed 1x laser + Avastin OS		
Max	**32**	**1,315**			**42**			

ROP= retinopathy of prematurity; BW= birth weight; GA= gestational age; += plus disease; SD= standard deviation; APROP= aggressive posterior ROP; SB= scleral buckle; OU= both eyes; OS= left eye; NDA= no data available

Once both groups had similar BW and GA, the apparent worst outcomes observed among referred patients (Group 2) could be partially explained by the delayed time for treatment. The calculated effect size of the difference in the PCA at treatment among both groups was 0.71 (95%CI: 0.02-1.38) which is a moderate effect, but considering the 95% confidence interval, it can reach to a large effect size.

Among the 24 treated patients at group 1, it was observed that 3 patients needed laser treatment twice to stop ROP progression. At group 2, two patients needed laser twice and also a scleral buckle procedure and one patient needed an antiVEGF intravitreous injection of bevacizumab (Avastin®) in order to stop ROP progression.

Comparing our data regarding the PCA at treatment for threshold ROP with the recent article published from Vietnam, as previous referenced, we observed that the PCA at treatment for inborn and for referred patients in that study were similar at 36.2 ± 2.3 weeks and 36.3 ± 2.2 weeks, respectively, while in our study the PCA for inborn was 37 weeks and the PCA for referred patients was 39 weeks, two weeks later, despite the lower BW and GA found in our patients[15]. It is well known, from the results of the Cryo-ROP, that ROP, prethreshold and threshold disease, usually occurs at completed 36 and 37 weeks of PCA, respectively. In this way, the inborn patients in our study were treated for threshold ROP in a median of 37 weeks of PCA, as postulated by the Cryo-ROP. The patients referred for treatment were treated in a median of 39 weeks of PCA, This is at least 2 weeks later that postulated by the Cryo-ROP Study[18,19].

Once both groups of patients in our study did not show differences regarding BW and GA, the only difference found in our study was the PCA at treatment. The delayed time for treatment could explain, in part, the worst outcomes observed among the patients referred for treatment.

A very interesting study from Ziakas et al., an audit of ROP screening in the Northern Region of England[20], related that 36% of the babies who were referred to different institutions developed threshold stage 3 disease. All those babies were under 27 gestational weeks and fewer than 859 g at birth, smaller babies when compared with the cohort of treated patients related in our study.

There were several patients whose functional outcomes could not be ascertained, especially in group 2 because parents had often moved to a different region or city.

The goal of screening programs is to prevent unfavorable anatomical and functional outcomes from ROP by detecting the more severe stages early enough to allow appropriate laser intervention even if babies need to be transferred to a different institution for ROP treatment.

It is very important to remark the short interval time between the identification of ROP and the appropriate time for successful treatment. Timing is critical because once the vitreous has become involved, or cicatrisation has commenced, retinal ablation by either cryotherapy or laser is ineffective. Treatment should therefore be undertaken as soon as possible, at least within 2-3 days of the identification of threshold disease[2].

Recently, telemedicine for early detection of ROP seems to be a better option than transferring sick premature babies only for expert examination and for treatment in order to save time. Telemedicine in ROP also alleviates the high rate of complications associated with the transfer of very sick preterm patients[21].

CONCLUSIONS

In this study, inborn patients were treated for ROP during the 37th week of PCA while referred patients were treated, usually, after the 39th week PCA. The worst outcomes observed among referred patients could be partially explained by the delayed time for treatment.

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