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Anatomical and refractive outcomes in patients with treated retinopathy of prematurity☆

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ABSTRACT

Objective: To describe the anatomical and refractive outcomes after treatment with intravitreal bevacizumab or laser in a patient cohort with retinopathy of prematurity (ROP).
Methods: A multicenter, prospective, and observational study was performed on patients with ROP treated at Hospital Roberto del Río. Those patients with less than 6 months of follow-up were excluded. Cases with posterior zone II, zone I ROP, and aggressive posterior ROP (AP-ROP) were treated with intravitreal bevacizumab. All other patients were treated with laser. Follow-up was performed every 3 months, and included fondo evaluation, refraction, and Teller tests.
Results: The treated group included 144 eyes of 72 patients, of whom 49 were treated with laser and 23 with intravitreal bevacizumab. One (1.4%) patient from the laser group progressed to stage 4 b retinal detachment and required bilateral vitrectomy. Of the remainder, 45 cases had type 1 ROP, 16 had threshold disease, and 11 had AP-ROP. The median of gestational age was 26 weeks (range 23–30), and median of birth weight was 800 g (range 405–1350). Median follow-up was 10 months (range 6–8). The Teller test median was 3.2 cycles/cm (range 0.32–13). There were 16 (22%) cases with a myopic refraction of −6 D or more. The sphere median was −1.75 D (range −16.00 to +3.50 D) and the cylindrical median was 0.00 (range −4.5 to +1.5 D). Anatomical success was achieved in 71 (98.6%) of patients.
Conclusion: Treatment with laser or intravitreal bevacizumab is a highly successful primary treatment for ROP. Anatomical success can be achieved in most cases. Treated patients develop frequent and severe refractive defects, which should be corrected. Vision outcome, measured using the Teller preferential test, shows good results.

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Resultados anatómicos y refractivos en pacientes tratados por retinopatía del prematuro

Palabras clave:
Retinopatía del prematuro
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RESUMEN

Objetivos: Describir los resultados anatómicos y refractivos en un grupo de pacientes tratados por retinopatía del prematuro (ROP) con bevacizumab intravítreo o láser.
Métodos: Estudio multicéntrico, prospectivo y observacional. Se incluyó a pacientes tratados por ROP en el Hospital Roberto del Río. Los pacientes con menos de 6 meses de seguimiento fueron excluidos. Los pacientes con zona II posterior, zona I o retinopatía agresiva posterior (AP-ROP) fueron tratados con bevacizumab intravítreo. El resto fueron tratados con láser. El seguimiento fue hecho cada 3 meses, e incluyó fondo de ojo, refracción y test de Teller.
Resultados: Se incluyeron 144 ojos de 72 pacientes. Un total de 49 fueron tratados con láser y 23 con bevacizumab. Un caso (1,4%) tratado con láser progresó a un desprendimiento de retina etapa 4b y requirió vitrectomía bilateral. Otros 45 casos tuvieron ROP de tipo 1; 16 enfermedad umbral y 11 AP-ROP. La mediana de edad gestacional fue de 26 semanas (rango 23-30) y la mediana de peso de nacimiento fue de 800 g (rango 405-1.350). La mediana de seguimiento fue de 10 meses (rango 6-28). La mediana del Teller fue de 3,2 ciclos/cm (rango 0,32-13). Del total, 16 casos (22%) presentaron miopía de −6 D o más. La mediana de la esfera fue de −1,75 D (rango −16,00 a +3,50 D) y la mediana del cilindro fue de 0,00 (rango −4,5 a +1,5 D). El éxito anatómico se logró en 71 pacientes (98,6%).
Conclusión: El tratamiento con láser o bevacizumab intravítreo como tratamiento primario en ROP es altamente eficaz. El éxito anatómico se alcanzó en la mayoría de los pacientes. Los resultados visuales obtenidos por test de Teller muestran buenos resultados.

Introduction

Retinopathy of prematurity (ROP) is a proliferative vascular disorder that could lead to legal blindness or severely impair vision in premature infants.[1] At present, first line of treatment includes retinal photocoagulation with diode laser and intravitreal antiangiogenics. In most cases, early treatment could prevent negative results secondary to ROP.[2–4] However, treated patients could also experience secondarily results such as visual of acuity, refraction or recurrence.[4–6]

The main objective of this study is to present the anatomical results of a series of patients treated for ROP. The secondary objective is to present the visual and refractive results of said group.

Methods

A multicenter,[b] prospective and observational study was carried out in compliance with the ethical principles of the Helsinki Declaration. The study included premature patients treated with laser photocoagulation or injections of antiangiogenics for treating ROP at the *Roberto del Río* Hospital. The study excluded treated patients who, at the time of closure of the study, did not have 6 months follow-up or missed regular checkups.

On the basis of the treatment criteria established by ETROP 3, treatment was indicated for ROP type 1 (any stage of ROP with plus disease in zone I, ROP in stage III in zone I without plus disease and ROP in stages 2 and 3 with plus disease in zone II), threshold disease (stage 3 with more than 5 continuous hours or 8 discontinuous hours) or posterior aggressive retinopathy (BH-ROP) (Fig. 1).[7] Patients with BH-ROP or retinopathies in posterior zone I or zone II were treated with antiangiogenics. The remaining cases were treated with laser. At surgery, all patients had ocular fundus documentation with RetCam 3 (Clarity Medical System, Pleasanton, CA, USA).

Treatments were performed by an ophthalmologist trained in ROP within 72 h from diagnostic. Laser treatment consisted in applying Nd:YAG 532-nm at a power of 180–400 mW utilizing half a separation space between dots. Antiangiogenic injections were administered with a paralimbar injection (0.5 mm) of bevacizumab, utilizing a dose of 0.625 mg (injection volume of 0.025 ml).

Demographic data and unfavorable anatomic results were considered, including retina detachment, retinal folds with macular compromise, tractional retrolental tissue, glaucoma, cataracts, hyphema and laser scars compromising the macula. After treatment, the patients were examined and followed by 2 ophthalmologists trained in ROP (D.O; M.Z). The patients were followed up according to the conventional screening criteria. After ROP regression, patients were checked at month

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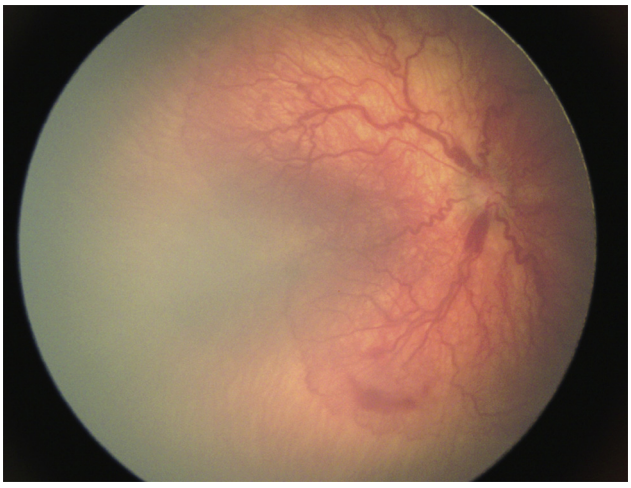

Fig. 1 – Ocular fundus photograph showing posterior aggressive retinopathy with plus disease in 4 quadrants.

one, 3 and 6 from treatment, evaluating cycloplegic refraction (45 min; use of 10 mg tropicamide [Mydriacyl 1%; Alcon, Fort Worth TX, USA], 25 mg phenylephrine chlorhydrate [Midfrin 2.5%; Alcon, Fort Worth, TX, USA], 2 applications at five-minute intervals) and ocular fundus. Subsequently, they were given appointments at 3-month intervals for the same assessments. Between follow-up month 6 and 12, visual acuity was measured with the Teller test. Data of both eyes of each patient were utilized for refractive comparison and statistical analysis. SPSS 16.0 was utilized for said purpose (SPSS Inc., Chicago, USA).

Results

The treated group included 144 eyes of 72 patients. Of these, 49 were treated with photocoagulation and 23 with bevacizumab. One patient (1.4%) of the group treated with laser involved to 4 b retina detachment and required bilateral vitrectomy. Overall, 15 cases presented with ROP in zone I, 13 in zone II posterior and 44 in zone II. Of all patients, 45 exhibited type I ROP, 16 exhibited threshold disease and 11 presented BH-ROP. The median of gestational age (GA) was 26 weeks (range 23–30) and the median weight at birth was 800 g (range 405–1350). The median follow-up was 10 months (range 6–28).

The median Teller test was 3.2 cycles/cm (range 0.32–13). In 16 cases (22%) myopia of -6D or greater was observed. Sphere median was −1.75 D (range −16.00 to +3.50 D). As regards cylinder, a median of 0.00 was observed (range −4.5 to +1.5 D). In 6 patients (8.3%) astigmatism above 2 D was observed. The spherical equivalent showed median of −0.5 D (range −16 to +3.50 D). Out of 145 eyes, 2 (1.4%) did not reach anatomic success (same patient, both eyes with retina detachment).

Table 1 shows the demographic comparison, GA median, median weight at birth and refractive results between ROP type 1, threshold ROP and BH-ROP. When comparing ROP type 1 with threshold ROP, a statistically significant difference was found for post-treatment sphere ($p = 0.007$) and a tendency to GA ($p = 0.06$) and weight at birth ($p = 0.09$), without finding differences in the remaining variables ($p > 0.05$). When comparing ROP type 1 with BH-ROP groups, a statistically significant difference was found for the post-treatment sphere ($p = 0.006$) and GA ($p = 0.01$), in addition to a tendency to weight at birth ($p = 0.07$), without differences in the remaining variables ($p > 0.05$). A comparison between patients treated with laser and 2 with bevacizumab is shown in Table 2, where a statistically significant difference was found for GA ($p = 0.01$) and birth weight ($p = 0.007$), in addition to a tendency toward post-treatment sphere ($p = 0.06$), without finding differences in the remaining variables ($p > 0.05$).

At the end of the follow-up period, anatomic success was achieved in 71 out of 72 patients (98.6%).

Discussion

The present study reports the anatomic and refractive results of a patient population treated for ROP, separating subgroups in ROP type 1, threshold ROP and BH-ROP. In this cohort, the anatomic result was favorable for the majority of patients (98.6%), whereas refractive results were comparable to those found in the literature.

In general, successfully treated ROP eyes exhibited a significant spherical refractive defect,[8,9] which is more significant in more aggressive ROP subgroups (threshold and BH-ROP).[9,10] Other studies reported that the prevalence of myopia is higher in treated groups, to the extent that patients with more aggressive ROP tend to exhibit higher prevalence of high myopia.[9] Evidence also demonstrates that patients with ROP in zone I treated with laser exhibit higher frequency of myopia and high myopia than those treated intravitreally.[11] In the present study, the refractive result did not show statistically significant differences in the group treated with laser versus the one treated with antiangiogenics (even though a tendency with a p value of 0.06 was obtained). A comparative analysis between zones was not carried out because in posterior zones I and II all patients were given bevacizumab injections. The severity of the myopic spherical defect was significantly higher in patients with BH-ROP and threshold ROP. No association between ROP severity and astigmatism was found, which is comparable to the ETROP studies.[12]

As in other studies, the present paper also reports a higher frequency of ROP in male patients[9,13] which does not have a clear explanation. Male prematures exhibit a higher frequency of hyaline membrane disease, which would point to a tendency toward higher oxygen requirements, a variable that was not measured in the present study.

BH-ROP is characterized by its posterior location together with prominence of plus disease and a poorly defined stage.[14] In contrast with other studies, all the patients with BH-ROP of this study were treated initially with intravitreal bevacizumab, the effectiveness of which has been demonstrated against laser for treating ROP in zone I.[7] However, as in patients with BH-ROP treated with laser, these also developed more significant spherical defects.[9] A study demonstrated that, at one year follow-up, the use of bevacizumab was associated to less myopia and astigmatism than with the use of laser.[15]

Table 1 – Comparison of demographic data, median GA, median weight at birth and refractive results for the various ROP types.

	ROP type 1 (n = 45)	Threshold ROP (n = 16)	BH-ROP (n = 11)
Females, n (%)	16 (35)	7 (43)	3 (27)
Gestational age (weeks)	26 (24–30)	25 (23–29)	25 (23–26)
Weight at birth (g)	830 (450–1.350)	773 (608–1.065)	772 (660–960)
Teller test (cycles/cm)	3.85 (0.32–6.5)	4 (1.6–6.5)	3.3 (0.64–3.20)
Sphere	−2 (+1.5 to −10.50)	−4.5 (0 to −12.50)[a]	−5.5 (−2 to −14)[a]
Cylinder	0 (0 to −4)	−0.5 (0 to −4)	0 (0 to −4)

[a] Statistically significant difference when comparing with ROP type 1 ($p < 0.05$).

Table 2 – Comparison between patients treated with laser and with bevacizumab.

	Bevacizumab (n = 23)	Laser (n = 49)
Females, n (%)	9 (39)	17 (35)
Gestational age (weeks)	25.2 (23 to 28)	26.2 (23 to 30)[a]
Weight at birth (g)	730 (536 to 960)	860 (450 to 1350)[a]
Teller test (cycles/cm)	3.2 (0.64 to 6.5)	3.2 (0.32 to 6.5)
Sphere	−2.21 (+1.5 to −14)	−3.46 (0 to −12.5)
Cylinder	−1.5 (0 to −4)	0 (0 to −4)

[a] Statistically significant difference when comparing with bevacizumab group ($p < 0.05$).

The present study exhibits limitations. Despite being a prospective study, it is not randomized and therefore the results of patients treated with bevacizumab and with laser cannot be compared. Even the indications for each treatment were for different patients. In addition, not all patients treated with intravitreal bevacizumab were examined with angiography after treatment. In contrast with patients treated with laser, the literature refers a significant frequent of ischemic angiographic alterations in patients treated with bevacizumab.[16] This matches the experience of the present group, for which reason at present all patients treated with bevacizumab are given appointments for angiographic examination. Recurrence in this subgroup is not infrequent, making strict follow-up necessary. Knowledge of the incidence, recurrence, risk factor and critical recurrence periods enables adaptations in the clinical management of these patients.[4]

In conclusion, primary treatment with laser or antiangiogenics is effective as it achieves anatomic success in the majority of patients. Regardless of the selected treatment, the high frequency of severe refractive defects make ophthalmological follow-up a crucial factor for obtaining the highest visual potential result for these patients.

Conflict of interest

The authors did not receive financial support and do not have commercial interests in the equipment.

REFERENCES

1. Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. Pediatrics. 2005;116:15–23.
2. Phelps DL, ETROP Cooperative Group. The Early Treatment for Retinopathy of Prematurity Study: better outcomes, changing strategy. Pediatrics. 2004;114:490–1.
3. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121:1684–94.
4. Mintz-Hittner HA, Geloneck MM, Chuang AZ. Clinical management of recurrent retinopathy of prematurity after intravitreal bevacizumab monotherapy. Ophthalmology. 2016;123:1845–55.
5. Axer-Siegel R, Maharshak I, Snir M, Friling R, Ehrlich R, Sherf I, et al. Diode laser treatment of retinopathy of prematurity: anatomical and refractive outcomes. Retina. 2008;28:839–46.
6. Yang CS, Wang AG, Sung CS, Hsu WM, Lee FL, Lee SM. Long-term visual outcomes of laser-treated threshold retinopathy of prematurity: a study of refractive status at 7 years. Eye. 2010;24:14–20.
7. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364:603–15.
8. Gunay M, Sekeroglu MA, Bardak H, Celik G, Esenulku CM, Hekimoglu E, et al. Evaluation of refractive errors and ocular biometric outcomes after intravitreal bevacizumab for retinopathy of prematurity. Strabismus. 2016;24:84–8.
9. Ruan L, Shan H-D, Liu X-Z, Huang X. Refractive status of Chinese with laser-treated retinopathy of prematurity. Optom Vis Sci. 2015;92:S3–9.
10. Quinn GE, Dobson V, Davitt BV, Wallace DK, Hardy RJ, Tung B, et al. Progression of myopia and high myopia in the Early Treatment for Retinopathy of Prematurity Study: findings at 4 to 6 years of age. J AAPOS. 2013;17:124–8.
11. Gunay M, Sukgen EA, Celik G, Kocluk Y. Comparison of bevacizumab, ranibizumab, and laser photocoagulation in the treatment of retinopathy of prematurity in Turkey. Curr Eye Res. 2016:1–8.
12. Davitt BV, Quinn GE, Wallace DK, Dobson V, Hardy RJ, Tung B, et al. Astigmatism progression in the early treatment for retinopathy of prematurity study to 6 years of age. Ophthalmology. 2011;118:2326–9.
13. Dhawan A, Dogra M, Vinekar A, Gupta A, Dutta S. Structural sequelae and refractive outcome after successful laser treatment for threshold retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 2008;45:356–61.

14. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123:991–9.
15. Harder BC, Schlichtenbrede FC, von Baltz S, Jendritza W, Jendritza B, Jonas JB. Intravitreal bevacizumab for retinopathy of prematurity: refractive error results. Am J Ophthalmol. 2013;155:1119–24.
16. Lepore D, Quinn GE, Molle F, Baldascino A, Orazi L, Sammartino M, et al. Intravitreal bevacizumab versus laser treatment in type 1 retinopathy of prematurity: report on fluorescein angiographic findings. Ophthalmology. 2014;121:2212–9.