






# Fundoscopic evolution of premature newborns with retinopathy of prematurity treated with intravitreal antiangiogenics

Evolução fundoscópica de recém-nascidos prematuros com retinopatia da prematuridade tratados com antiangiogênicos intravítreos

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## ABSTRACT

**Objective:** To determine the evolution of retinopathy of prematurity in patients treated with intravitreal antiangiogenics in the retina private practice.

**Methods:** A retrospective descriptive observational case series study was conducted. The study was non-experimental and non-probabilistic. Based on a population of 61 newborns, with a 99% confidence interval and a margin of error of 1%, the sample would be 61 newborns. The data from Google Sheets was transferred to CVS and then the Statistical Package for the Package Power was used for data analysis. Microsoft Word and Google Docs were used as information processors. When intravitreal injections are used to treat retinopathy of prematurity, positive results, stage improvements, and retinopathy of prematurity regression are expected.

**Results:** Based on our results, we were able to conclude that patients treated from stage I to stage IV had a significant regression of their pathology in a range of 90% to 100% post-treatment with anti-VEGF. Our study does not include patients with stage V, and no correlation was found between the stage of ROP and the degree of prematurity at birth (P-value = 0.312).

**Conclusion:** Patients treated from stage I to stage IV had a significant regression of their pathology in a range of 90% to 100% post-treatment with anti-vascular endothelial growth factor. Our study does not include patients with stage V, and no correlation was found between the stage of retinopathy of prematurity and the degree of prematurity at birth.

## RESUMO

**Objetivo:** Determinar a evolução da retinopatia da prematuridade em doentes tratados com antiangiogênicos intravítreos num consultório privado de retina.

**Métodos:** Foi realizado um estudo observacional descritivo retrospectivo de série de casos. O estudo foi de natureza não experimental e não probabilística. Com base numa população de 61 recém-nascidos, com um intervalo de confiança de 99% e uma margem de erro de 1%, a amostra seria de 61 recém-nascidos. Os dados do Google Sheets foram transferidos para o CVS e, em seguida, utilizou-se o pacote estatístico SPSS para a análise dos dados. O Microsoft Word e o Google Docs foram utilizados como processadores de informação. Quando as injeções intravítreas são utilizadas para o tratamento da retinopatia da prematuridade, esperam-se resultados positivos, melhorias no estágio e regressão da retinopatia da prematuridade.

**Resultados:** A partir dos nossos resultados, pudemos concluir que os doentes tratados do estágio I ao estágio IV apresentaram uma regressão significativa da sua patologia numa faixa de 90% a 100% após o tratamento com anti-VEGF; o nosso estudo não inclui doentes com estágio V, e não foi encontrada correlação entre o estágio da ROP e o grau de prematuridade ao nascimento (P-value = 0,312).

**Conclusão:** Os pacientes tratados desde o estágio I ao estágio IV apresentaram uma regressão significativa da sua patologia numa faixa de 90% a 100% após o tratamento com antifator de crescimento endotelial vascular; o nosso estudo não inclui doentes com estágio V, e não foi encontrada qualquer correlação entre o estágio da retinopatia da prematuridade e o grau de prematuridade ao nascimento.



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## INTRODUCTION

Retinopathy of prematurity occurs due to the growth of abnormal new vessels in the retina, affecting premature babies or those born with less than 1,500 g, which, if treated in time, prevents blindness.<sup>(1)</sup> It is classified according to the affected areas, stage, and extent of the pathology. The acute stage includes stages 1 to 3, in which the development of the retina is incompletely vascularized. For retinal detachment, we will see included stages 4 and 5, in which stage 4 is partial detachment and stage 5 is complete detachment of the retina.<sup>(2)</sup>

A baby is considered premature when they are born alive before reaching 37 weeks of gestation. Premature babies will be divided according to gestational age ranges into extremely premature babies (< 28 weeks), very premature babies (29 to 32 weeks), and moderate to late premature babies (33 to 37 weeks).<sup>(3)</sup> Eight per cent of newborns in the Dominican Republic are born prematurely.<sup>(4)</sup>

Premature babies must comply with a protocol at the time of birth; usually, they must be taken to the neonatal intensive care unit (NICU), where they are usually administered a series of medications, blood transfusions, and oxygen therapy, depending on their needs, to improve their survival rate.<sup>(5)</sup>

The treatment of Retinopathy of prematurity (ROP) will depend on the case or the patient's stage; certain cases are mild enough and improve without treatment.<sup>(1)</sup> Among the treatments we can find are laser photocoagulation, anti-vascular endothelial growth factor (anti-VEGF) therapy, and cryotherapy. In some stages, the patient might need a vitrectomy, and cerclage can also be used in cases of retinal detachment.<sup>(6)</sup>

Anti-VEGF is an intravitreal injected medication that blocks vascular endothelial growth proteins. It is used to block the formation of new abnormal vessels, thus preventing vision loss. Currently, we can find three types: aflibercept, ranibizumab, and bevacizumab, the latter being the most used treatment in ROP, commercially known as Avastin.<sup>(7)</sup> Among the unfavorable effects that anti-VEGF treatment may present are retinoschisis, persistent avascular retina, and long-term macula abnormalities.<sup>(2)</sup>

It has been shown that treatment with anti-VEGF was associated with higher retreatment compared to the use of laser photocoagulation; among the anti-VEGFs studied, ranibizumab was found to have a higher rate of recurrence and retreatment than bevacizumab, aflibercept, and conbercept.<sup>(8)</sup> In another study conducted by Patel et al. in 2024,<sup>(9)</sup> the higher the dose of bevacizumab, the lower the amount of retreatment.<sup>(9)</sup> The patients seen in this study were treated with 0.025 mL of bevacizumab.

It was also observed that the use of anti-VEGF has fewer complications than laser photocoagulation therapy, among which the incidence of myopia, retinal detachment, and retinal detachment.<sup>(8)</sup>

The purpose of this research is to determine the evolution of retinopathy of prematurity in patients treated with intravitreal antiangiogenics in the retina private practice at an Ophthalmology Center from January 2020 to January 2023.

## Complications

After ROP resolves, myopia, strabismus, amblyopia, late vitreous hemorrhage, ROP reactivation, and retinal detachment may develop, the latter of which, in certain cases, may occur before the retinopathy resolves.<sup>(1)</sup>

### Myopia

Myopia is a defect in the way light is reflected inside the eye, causing distant objects to appear blurry. This occurs when light focuses in front of the retina instead of on it.<sup>(10)</sup>

Some of the symptoms that may be present are problems seeing distant objects, squinting to clarify vision, and eye fatigue. Some patients may also experience headaches.<sup>(10)</sup>

### Strabismus

Strabismus is a disorder in which one of the eyes is not aligned in the same direction as the other eye. This occurs when the muscles that allow each eye to move do not work together, and both eyes are looking at different objects, thus confusing the brain and eventually suppressing the image from the eye that is considered weaker.<sup>(11)</sup>

### Amblyopia

Amblyopia, also known as lazy eye, refers to the loss of the ability to see clearly through one eye. This usually occurs when the nerve pathway from the eye to the brain is damaged and the brain cannot recognize the vision from the affected eye, resulting in an abnormal or distorted image.<sup>(12)</sup>

### Retinal detachment

Retinal detachment is the separation of the neurosensory layer from its underlying pigmented layer.<sup>(13)</sup> The most common cause of detachment is a tear in the retina itself.<sup>(14)</sup>

There are approximately three types of detachment:

- Rhegmatogenous: this involves a tear in the retina and is usually the most common type:
  - Risk factors include myopia, cataract surgery, trauma, and retinal degeneration, among others.<sup>(14)</sup>

- Traction: this may be due to vitreoretinal traction caused by preretinal fibrous membranes that can be found in various diseases.<sup>(14)</sup>
- Serous or exudative: it occurs due to fluid transudation into the subretinal space. This can be caused by severe uveitis, hemangiomas, and choroidal cancers, among others.<sup>(14)</sup>

### Late vitreous hemorrhage

This is bleeding in the vitreous humor that can present with floaters, blurred vision, or sudden vision loss caused by trauma, surgery, vascular problems, or underlying conditions such as diabetic retinopathy and retinopathy of prematurity. Vision loss occurs because light cannot pass through the vitreous humor.<sup>(15)</sup>

### Reactivation of Retinopathy of prematurity

Reactivation of retinopathy of prematurity is a possible complication after treatment with anti-VEGF, which may be related to the dose of the medication, specifically more than two injections; recent studies explain that it commonly occurs one year or a year and a half after postmenstrual age. The new extra-retinal vessels are delicate compared to those in acute ROP, which makes visualization of the vessels difficult. Reactivation may progress to fibrosis, contraction, and ultimately retinal detachment.<sup>(2)</sup>

## METHODS

A retrospective, descriptive, observational, case series-type study was conducted. The sampling is non-experimental and non-probabilistic. Using a population of 61 newborns, a confidence interval of 99%, and a margin of error of 1%, the sample to be used was 61 newborns.

Our selection criteria were based on premature babies who attended the retinopathy of prematurity appointment at the Ophthalmology Center in the period from January 2020 to January 2023, who received 1 or more doses of anti-VEGF in one or both eyes, and who continued their consultations at the center.

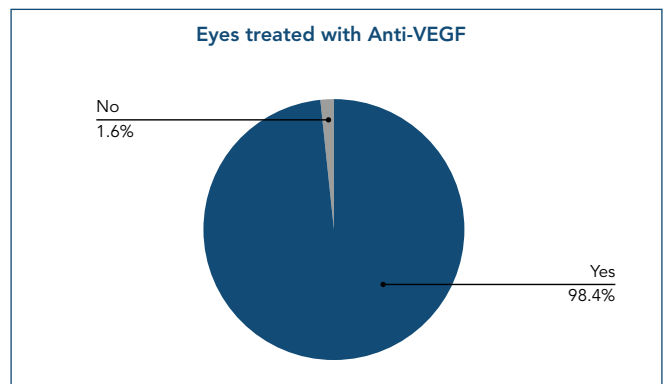
Two of our four specific objectives were to correlate the stage of ROP with the efficacy of anti-VEGF treatment and to contrast the relationship between the stage of ROP and the degree of prematurity, so we took into account the stages of ROP, degree of prematurity, and the amount of anti-VEGF doses applied in our inclusion criteria.

The researchers completed a questionnaire for the medical records. Subsequently, the data was extrapolated from Google Sheets to CVS and then Statistical Package

for the Social Sciences (SPSS) for data analysis. Microsoft Word and Google Docs were used as data processors.

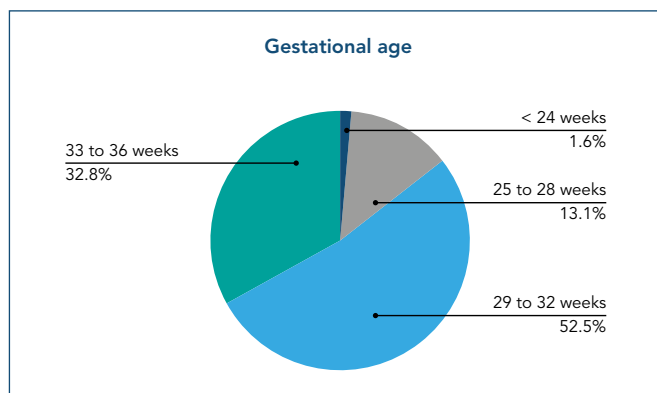
## RESULTS

- Of the 61 patients who met our inclusion criteria, 59% were female and 41% male, for a total of 122 eyes, of which 98.4% required anti-VEGF therapy (Figure 1).
- It was determined that most of the eyes presenting with retinopathy of prematurity were very preterm patients, ranging from twenty-eight<sup>(4)</sup> to thirty-two<sup>(9)</sup> weeks of gestation, with 51%; 36% of the eyes were associated with moderate or late prematurity, and 13% were related to extreme prematurity (Figure 2).
- 72% of patients remained on oxygen therapy for more than five days, and 28% for less than five days (Figure 3); of these, 54% used CPAP, 25% used an oxygen hood, and 21% required mechanical ventilation (Figure 4).
- Other risk factors included red blood cell transfusions, with 82% of patients not receiving transfusions, while 18% did; 77% of infants did not develop sepsis, and 23% did (Figure 5).
- Within the treated stages, we observed that in stage I, there was a 100% regression of ROP, emphasizing that these patients are not treated unless they present in conjunction with plus and pre-plus disease; as well as 38 of the 39 eyes in stage II of ROP, and 39 of 43 patients in stage III presented regression of the pathology, for a total of 89 of 93 eyes in stages I to III presented a stable regression of ROP post-treatment. In Stage IV, 98% of the treated eyes showed regression of ROP (Table 1 and Figure 6).
- In our sample, no patients with stage V were found.
- There was no statistical significance in the correlation of the anti-VEGF treatment with the ROP stage (Chi-squared test p-value = 0.312).

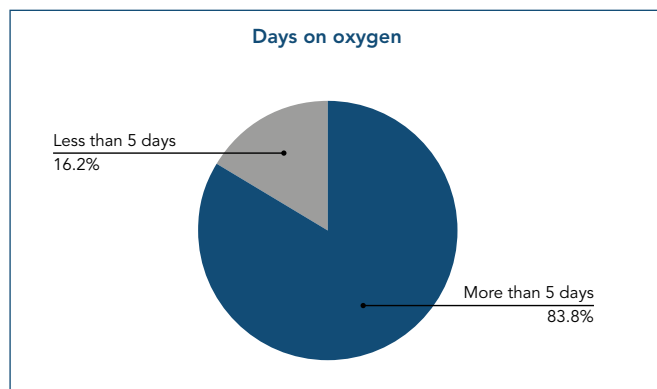


Anti-VEGF: anti-vascular endothelial growth factor.

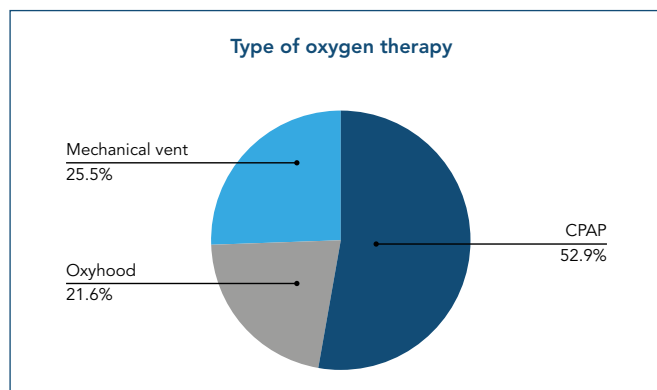
**Figure 1.** Sample distribution according to the number of eyes treated in the retina practice of the Ophthalmology Center.



**Figure 2.** Sample distribution of gestational age at birth of patients attending the retina practice at Ophthalmology Center.



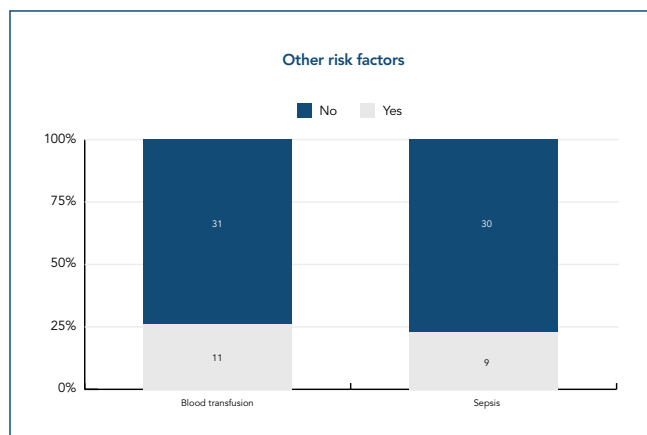
**Figure 3.** Sampling distribution of the number of days the newborn received oxygen therapy during hospitalization.



**Figure 4.** Sampling distribution of the type of oxygen therapy that the newborn received during hospitalization.

## DISCUSSION

In 2010, according to estimates, approximately 184,700 babies out of 14.9 million were born prematurely and developed some stage of ROP, for which they received intravitreal antiangiogenic therapy.<sup>(16)</sup> In a prospective comparative study, 174 eyes of 87 premature babies were examined, all of whom were diagnosed with grade 3 ROP and randomly assigned to receive anti-VEGF therapy.<sup>(17)</sup> Of the 122 eyes included in our research, 120 eyes used intra-vitreal antiangiogenic therapy (Figure 1).

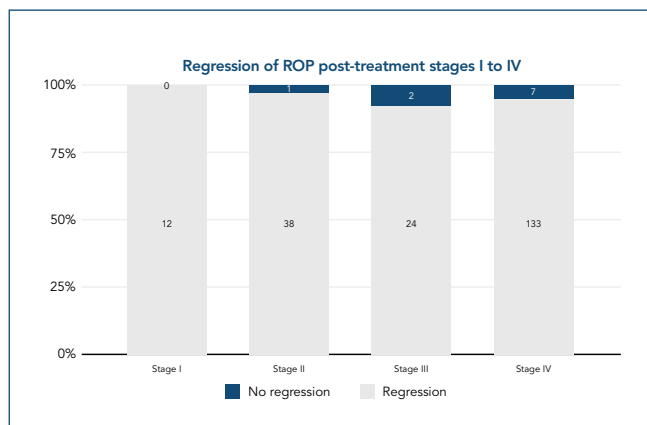


**Figure 5.** Sample distribution of the number of newborns who suffered from sepsis, who received blood transfusions, and other risk factors.

**Table 1.** Regression of ROP in stages I to IV

	Stage I	Stage II	Stage III	Stage IV	Total
No regression	0	1	4	2	7
Regression	12	38	39	24	133
Total	12	39	43	26	140

This table represents the eyes in stages I to IV that presented post-treatment regression of the pathology. There were no patients with stage 5 ROP. Patients with stage 4 demonstrated a 92% regression.



**Figure 6.** Regression of post-treatment ROP in stages 1 to 4.

A study conducted in 2015 involving 80 premature infants found that most patients had a gestational age of  $26.4 \pm 1.5$  weeks, with 6.2% having an active form of ROP.<sup>(18)</sup> We determined that all of our patients had active ROP and that 52.5% of our patients were between 29 and 32 weeks of gestational age (Figure 2).

In a study conducted by Curbelo in 2015,<sup>(19)</sup> 88.2% of premature infants who used oxygen developed ROP. 60.7% of our patients used oxygen therapy. Patients with active ROP required a longer duration of oxygen therapy ( $20 \pm 3.4$  days) compared to those without ROP, who had a shorter duration of oxygen therapy. Twenty-eight percent of our patients remained on oxygen therapy for more than 5 days (Figure 3). A study by Kim et al. in 2015<sup>(20)</sup> revealed

that the use of mechanical ventilation and CPAP is a risk factor and a guaranteed referral to an ophthalmologist. Of our patients, 54% used CPAP, 25% used an oxyhood, and the remaining 21% used mechanical ventilation (Figure 4).

Other risk factors include neonatal sepsis and blood transfusions, which accelerate oxidative damage, causing ROP.<sup>(20)</sup> Twenty-three percent of our patients developed neonatal sepsis (Figure 5), and 18% of our patients received red blood cell transfusions (Figure 5).

The study by Atrata et al. in 2012<sup>(17)</sup> showed stable regression of ROP in 90.2% of patients treated with anti-VEGF therapy who had stage 3 disease in zones 1 and/or 2. Our patients with stage 1 to 4 ROP post-tx had a regression of 77.14%, with a p-value of 0.312 (Table 1, Figure 6).

## CONCLUSION

Anti-VEGF therapy demonstrated high efficacy in inducing regression of retinopathy of prematurity across stages I to IV, with particularly favorable outcomes in early disease. The majority of affected eyes were observed in very preterm neonates. Although regression rates were consistently high, statistical analysis did not reveal a significant correlation between ROP stage and treatment response ( $p = 0.312$ ), suggesting that therapeutic benefit is broadly applicable across disease stages.

Beyond gestational age, several neonatal risk factors were identified. A substantial proportion of patients (72%) required oxygen therapy for more than five days, with varying modalities including CPAP (54%), oxyhood (25%), and mechanical ventilation (21%). Additional factors included red blood cell transfusions (18%) and sepsis (23%), both of which were present in a minority of cases. No cases were observed in stage V, which highlights that early treatment and diagnosis helps prevent the progression to advanced disease.

## AUTHOR'S CONTRIBUTION

Camila Sofia Negrin: Conceptualization (lead), data curation (equal), methodology (equal), formal analysis (equal), investigation (equal), project administration (lead), software (supporting), writing-original draft (equal), writing-review and editing (equal); Dolly Chantal Ruiz-Garcia: Conceptualization (supporting), data curation (equal), methodology (equal), formal analysis (equal), investigation (equal), project administration (supporting), software (lead), writing-original draft (equal), writing-review and editing (equal); Carmen Rosina Negrin Martin: Resources (lead), supervision (supporting), validation (equal), writing - review and editing (supporting); Aderina

Maldonado: Resources, supervision (supporting), validation (equal), writing - review and editing (supporting); Michael Alcantara Minaya: Supervision (supporting), validation, visualization, writing -review and editing (supporting).

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