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Retinopathy of Prematurity: Treatment-Needed Patients, Treatment Complications, and Recurrence Rate

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Abstract

Background: The prevalence of Retinopathy of Prematurity (ROP) is rising in Iran. We aimed to evaluate the clinical and demographic characteristics of ROP infants who need treatment, the type of treatment, and the complications in the years 2018 to 2022.

Methods: This is a cross-sectional study. We evaluated the patient's electronic medical records from 2018 to 2022. The required data was extracted from the registry dataset, including demographics, clinical characteristics of infants who required treatment, and the type and severity of treatment-related complications.

Results: From 10,159 infants referred to the retinopathy of prematurity clinic from the beginning of 2018 to 2022, 5008 subjects (49.29%) were suffering from ROP, among whom 416 (8.3%) patients needed treatment for ROP. The mean ± Standard Deviation (SD) of birth age and birth weight were 28.66 ± 2.24 weeks and 1227.24 ± 375.97 grams. While most of our patients (742 eyes, 96.4%) underwent Intravitreal Bevacizumab (IVB) injection as the treatment modality, laser photocoagulation was performed for 25 eyes. Four eyes received pars plana vitrectomy treatment. The recurrent disease occurred in 23 patients (44 eyes). Birth age, birth weight, and the time of oxygen therapy were significantly different between the treatment responders and the neonates who experienced the recurrent disease.

Conclusion: In this study, we showed that the birth age and weight of neonates who experienced a relapse were significantly lower. Besides, the results of treatment with IVB injection were satisfactory, with a relatively low recurrence rate and minimal complications.

Key Words: Anti-VEGF, Birth age, Birth weight, Intravitreal injection, Retinopathy of prematurity, Treatment.

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1- INTRODUCTION

Retinopathy of prematurity (ROP) is caused by abnormal retinal vasculogenesis in premature infants (1). Although it is usually mild and resolves spontaneously with minimal sequelae, vision-threatening complications could occur in any case (2). Therefore, all preterm infants are at risk for ROP, and low birth weight, oxygen therapy, and hypoxia are among the most significant risk factors (3). The etiopathogenesis of the disease includes two phases. Retinal vascularization is stopped as a result of growth factors downregulation, such as Vascular Endothelial Growth Factor (VEGF), due to hyperoxia, and loss of maternal-fetal interaction (phase 1). Subsequently, the non-perfused area of the retina promotes growth factor-induced vasoproliferative (phase 2), which might result in blinding complications such as tractional retinal detachment (TRD) (1, 3).

We summarized the key elements in the disease classification in terms of prognosis and pathophysiology in table 1 (4).

The prognosis is worsened, and the likelihood that therapy would be necessary is increased by a wider retinal avascular area (zone 1), a more advanced stage of the illness, and the existence of the plus disease (5). Various treatment options have been proposed to prevent vision-threatening complications in ROP. In the 1980s, cryotherapy of the avascular retina was the procedure of choice for treating ROP (6). After that, laser photocoagulation of the non-perfused retina becomes popular and is the treatment of choice in some patients (7, 8). Recently, novel approaches, including anti-VEGF intravitreal injection, have garnered interest (9). Vascular Endothelial Growth Factor (VEGF) is the root cause of retinal neovascularization. Anti-VEGF therapies may, therefore, be helpful in the management of ROP. Bevacizumab is a recombinant human monoclonal antibody that acts on all VEGF isoforms (10). Various studies have shown that the complications of ROP treatment include infection, intraocular inflammation and retinal detachment, and vitreous or retinal bleeding (11). The side effects of anti-VEGF in ROP have been reported very rarely, including respiratory failure, thrombotic complications, liver disorders, upper respiratory infections, and nephropathy (12, 13).

The likelihood that premature children will survive has improved in recent years in developing nations, including Iran, as a result of improvements in general health and disease management. So, the prevalence of ROP cases is also rising (14).

This study aims to evaluate the clinical and demographic characteristics of ROP infants who need treatment, the type of treatment, and the complications from 2018 to 2022.

2- MATERIALS AND METHODS

This is a cross-sectional study. We evaluated the patient's electronic medical records from 2018 to 2022. The required data was extracted from the registry dataset, including demographic and clinical characteristics of infants who required treatment, along with the type and severity of treatment-related complications.

2-1. Examination protocol

The ROP clinic of Khatam Al-Anbia Eye Hospital is a tertiary referral center and the only center in this field in the northeast of Iran. All premature neonates who need retinal examination based on national guidelines are imaged in this center using the RetCam device after dilating the pupils. Images and demographic data of patients, including gestational age and birth weight, are recorded in the registry software.

2-2. Treatment protocol

In this center, there are two treatment options for ROP neonates, which include laser photocoagulation of avascular retinal areas and intravitreal injection of bevacizumab (0.625 mg in 0.025 ml). When deciding on a course of treatment, the essential considerations include the severity of the disease, the infant's present age, the gestational age at birth, and the attending physician's recommendation. Older age in the presence of shunt vessels and vascular loops at the border of vascular and avascular areas leads the doctor to choose laser as a treatment option. Based on the results of previous studies, Intravitreal Bevacizumab (IVB) injection is not considered an option for rescue treatment in recurrent disease in patients with a history of laser photocoagulation.

2-3. Data analysis

For statistical analysis, we utilized IBM SPSS Statistics, Statistical Package for Social Sciences, version 22 (IBM Corporation, Chicago, IL). To examine the data distribution, we applied the Shapiro-Wilk test. The participants' features are described using descriptive statistical techniques, such as central and dispersion indices. The independent samples t-test, or its non-parametric equivalent, was used to compare the quantitative variables between the groups. The chi-square test was employed to examine the association between the qualitative factors. P-values less than 0.05 were regarded as significant in all calculations.

3- RESULTS

In 2018 to 2022, 10,159 neonates were referred to the ROP clinic, among whom 5008 (49.29%) were diagnosed with ROP. Based on the examination results, 416 patients (771 eyes) needed treatment for ROP, which were 8.3% of ROP patients. The average number of visits was 12.31 ± 5.70. The mean ± Standard Deviation (SD) of birth age was 28.66 ± 2.24 weeks. The mean ± SD of birth weight was 1227.24 ± 375.97 grams. The average oxygen therapy time of the patients was 15.51 ± 19.28 days. Most of the patients who needed treatment (287 people, 69.7%) were singletons; and 26.5% (109 people) were twins (**Table 1**).

Table-1: ROP classification

Variable	Explanation
Location	Zone I: Retina in a circle with a radius twice the distance from the center of the macula to the center of the disc. Zone II: donut-shaped area from the borders of Zone I to nasal ora serrata Zone III: Remaining crescent-shaped area of the temporal retina
Extent	Number of clock-hour involved
Severity	Stage 0: immature retinal vascularization without any pathologic changes Stage I: Demarcation line between the normal and avascular retina Stage II: Demarcation ridge between the normal and avascular retina Stage III: Presence of extraretinal fibrovascular proliferation Stage IV: Partial retinal detachment Stage V: Total retinal detachment
Plus disease	Venous dilatation and arteriolar tortuosity in at least two quadrants of the posterior retina

The mean ± SD of the patient's gestational age and body weight at the time of treatment were 36.37 ± 2.97 weeks and 2082.08 ± 753.01 grams, respectively. We summarized the clinical characteristics of ROP eyes, including the zone and severity stage of the disease in neonates who underwent treatment in **Table 2**.

Table-2: Clinical characteristics of ROP patients who underwent treatment

Variable		Number of eyes (%)
Location	Zone I	210 (27)
	Zone II	535 (69)
	Zone III	26 (4)
Severity	Stage 0	43 (5.5)
	Stage 1	139 (18.5)
	Stage 2	395 (51)
	Stage 3	189 (24)
	Stage 4	4 (0.5)
	Stage 5	1 (0.1)
Plus disease	Plus disease	572 (74.2)

As presented in **Table 2**, most patients who needed treatment were in the severity stages 2 and 3 (75%), in most of whom the vascularization ended in zone 2 (69%). The point to be noticed is that 26 eyes with the involvement of zone III, and 182 eyes with lower severity stages (stages 0 and 1) needed treatment.

While most of our patients (742 eyes, 96.4%) underwent IVB injection as the treatment modality, laser photocoagulation was performed for 25 eyes. And four eyes received pars plana vitrectomy treatment.

The recurrent disease occurred in 23 patients (44 eyes). The average interval between the treatment and reactivation of the disease was 60.58 ± 29.06 days. Rescue treatment included IVB (11 eyes), laser photocoagulation (23 eyes), pars plana vitrectomy (1 eye), and scleral buckle surgery (1 eye).

The study's findings revealed a significant association between birth age and the recurrence of ROP (P=0.001). The average age at birth of those who had relapses was substantially lower than that of individuals who had not. Additionally, the patients who relapsed had significantly lower birth weights than those who did not (P = 0.01). The survey results revealed that those who received oxygen treatment for a longer time were substantially more likely to experience a recurrence (P=0.01), even though there was no significant correlation between the average stay in the NICU and the recurrence of ROP (**Table 3**).

Table-3: Comparison of birth age, birth weight, oxygen therapy time, and ICU hospitalization time in infants with recurrent ROP and complete treatment response

Variable	Recurrent disease		P-Value
	Yes	No	
Gestational age at birth (weeks) (mean ± SD)	26.74 ± 1.66	28.75 ± 2.22	0.001
Birth weight (grams) (mean ± SD)	1019.33 ± 286.98	1236.96 ± 377.11	0.010
Time of oxygen therapy (days) (mean ± SD)	25.79 ± 21.77	19.05 ± 15.02	0.010
Duration of hospitalization in NICU (days)	39.53 ± 15.42	33.14 ± 18.97	0.14

Considering the complications following the treatment, three patients developed iatrogenic cataracts after IVB injection, and one patient developed vitreous hemorrhage following laser photocoagulation. We had no case of endophthalmitis. No systemic complications observed.

4- DISCUSSION

From 10,159 neonates referred to the ROP clinic from 2018 to 2021, 5008 subjects (49.29%) were suffering from ROP, of which 416 patients (8.3%) needed treatment. In this study, the most selected treatment modality was IVB injection (96.4%) compared to laser photocoagulation (3%). Besides, pars plana vitrectomy was performed in 4 eyes due to the advanced stage of ROP. The frequency of ROP and the number of cases necessitating ROP treatment are rising in Iran, due to improvements in the country's healthcare system and the rise in the survival rate of premature newborns (14, 15).

In a study in 2021, 92 (80%) of 114 infants with ROP who received treatment underwent laser therapy, while 20% received IVB injections (16). Gupta et al. in 2016, investigated 722 neonates with ROP. 9.5% of their patients were treated with laser photocoagulation or IVB injection (17). The prevalence of patients requiring treatment in this study was close to ours. Because of the successful treatment experience with intravitreal injection of anti-VEGF agents based on the results of previous studies(18, 19) and the possibility of continued vascularization and tissue preservation compared to laser photocoagulation, the trend to use this treatment method in premature infants has been increased (20, 21).

Administration of the anti-VEGF agents could potentially lead to a delay in the normal vascularization process (22). Furthermore, Recurrence of ROP occurs later in infants treated with intravitreal anti-VEGF injection and may occur up to 16 weeks after treatment, which shows the importance of long-term follow-up examinations after treatment with the intravitreal injection (23, 24). Chen et al., in 2022, investigated the recurrence rate of ROP after treatment with 0.3 mg and 0.25 mg of ranibizumab in China. This study was conducted on 146 eyes of 82 patients. Although the results of the study showed that a higher dose of ranibizumab is associated with a lower rate of recurrence, the within comparison group revealed that the recurrence rate of ROP is significantly lower in neonates with higher gestational ages at birth ($p<0.05$) (25), which is consistent with the results of our study. We showed that the average birth age of infants who experienced recurrency was significantly lower than that of subjects who completely responded to treatment ($P=0.001$). Mirghorbani et al., in 2022, investigated the clinical course of retinal vascularization in ROP patients treated with IVB injection. They showed that recurrent disease occurs significantly higher in neonates with pre-treatment ROP zone I, compared to patients with zone II and III involvements. Furthermore, factors such as the birth age of fewer than 30 weeks, twin birth, the presence of anemia, and a history of phototherapy and intubation have a significant adverse effect on the treatment response. In their study, no significant relationship was found between oxygen therapy and recurrence rate, which is not consistent with the results of our study (26). In our study, lower birth age, lower birth weight, and a longer duration of oxygen-therapy were significant risk factors for disease recurrency which should be considered in scheduling follow-up in ROP patients. However, the recurrence rate was satisfactory (5.7% of the treated eyes). Regarding the average interval between the first treatment trial and the disease reactivation, which was about 60 days,

discontinuation of follow-up examinations in ROP patients treated with IVB should be done with caution and after ensuring complete retinal vascularization.

In this study, one patient experienced vitreous hemorrhage following laser therapy, and three patients who received IVB injections acquired cataracts (iatrogenic cataracts). The paucity of long-term follow-up prevents us from discovering more about the treatment-related complications. Various studies have documented several ROP treatment-related complications in long-term follow-up. Endophthalmitis is one of these complications. However, this issue is relatively uncommon (27). In this study, we had no case of post-IVB injection endophthalmitis. Another complication mentioned in the studies is cataracts, which is a serious blinding disease when occurring in infancy (8). Cataracts can occur after laser treatment of ROP or after anti-VEGF injections. In the ETROP study, cataracts occurred in 1.2% of eyes receiving laser photocoagulation (8). The mechanism of cataract formation after the laser is related to the rising of the lens protein temperature. Laser energy absorption by the iris or tunica vasculosa lentis is a proposed mechanism for overheating the lens proteins. The wavelength of the laser is an essential contributor. Infrared laser energy has the least absorption by vascular structures, so the tunica vasculosa lens is not affected by this wavelength. In contrast, the 532 nm green laser is effectively absorbed by vascular tissues. This difference likely explains why the incidence of cataracts reported with green lasers is higher than that of cataracts with infrared lasers (28, 29). Cataracts are likely to occur after intravitreal injections due to mechanical trauma with the lens and turbulence in the vitreous following the injection (30). The larger lens size compared to the eye and less space for injection from the pars plana in neonates are predisposing factors to contact with the lens during the injection. We showed that traumatic cataracts in patients receiving IVB injections are relatively rare, with an incidence of less than 0.5%.

4-1. Limitations of the study

This study has some limitations. The absence of treatment comparisons and the lack of long-term patient follow-up constitute two of the study's most serious shortcomings.

5- CONCLUSION

In this study, we showed that the birth age and weight of neonates who experienced a relapse were significantly lower. Besides, the results of treatment with IVB injection were satisfactory, with a relatively low recurrence rate and minimal complications.

6- ETHICAL CONSIDERATIONS

This study was approved by the ethics committee of Mashhad University of Medical Sciences, which adhered to the Declaration of Helsinki (approval number: IR.MUMS.MEDICAL.REC.1399.266). Informed consent was obtained from the patients.

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