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Original Research

Evaluation of Treatment Models in the Treatment of Retinopathy of Prematurity

Semra Tiryaki Demir,[1] Dilek Güven,[1] Murat Karapapak,[1] Hasan Sinan Uslu,[2] Ali Bülbül,[2] İbrahim Çağrı Türker,[3] Selam Yekta Şendül,[1] Burcu Dirim[1]

[1]Department of Ophthalmology, Sisli Etfal Training and Research Hospital, Istanbul, Turkey
[2]Department of Neonatology, Sisli Etfal Training and Research Hospital, Istanbul, Turkey
[3]Department of Ophthalmology, Lutfiye Nuri Burat State Hospital, Istanbul, Turkey

Abstract

Objectives: This study aims to evaluate the treatment modalities applied for retinopathy of prematurity (ROP) and to determine the efficacy and results of treatment modalities.

Methods: Premature babies, who needed treatment for ROP and followed-up in the Neonatal Intensive Care Unit (NICU) of our hospital or external centers, were retrospectively evaluated between January 2012 and January 2017. According to the criteria determined by the International ROP committee, the zones and stages of the cases were recorded. In this study, patients were evaluated in three groups. Group 1: plus disease with any stage in zone 1, group 2: plus disease in zone 2, together with stage 2 or 3, group 3: classified as aggressive posterior retinopathy (APROP). The birth weight, gestational age, treatment weeks and treatments that were administered were recorded. Regression in plus disease, macular dragging and retinal detachment did not develop were evaluated as successful treatment.

Results: 1746 preterm babies were examined. 65 (3.7%) preterm babies were included in this study, 31 female and 34 male. 126 eyes of preterm babies were intervened. The mean birth weight was 1159 (535-2200) grams, and the mean gestational age was 28.4±2.5 (24-34) weeks. Group 1 had 33 eyes (26.1%), group 2 had 71 eyes (56.3%), and group 3 had 22 eyes (17.4%). 94 eyes (74.6%) were treated once, 26 eyes (20.6%) were treated twice, 6 eyes (4.8%) received treatment three times. The first treatment was applied at 36±2.4 (32-41) weeks. The first treatment was performed with intravitreal bevacizumab (IVB) in 75.8% of group 1 and 95.5% of group 3, and with diode laser photocoagulation (LPC) in 78.9% of group 2. There was a significant correlation between birth week and birth weight and first treatment week. Re-treatment was applied to 32,8% in LPC group and 19.2% in the IVB group due to recurrence. 5 eyes which were applied LPC+IVB did not need any re-treatment. Stage 4a retinal detachment developed in both eyes of 1 patient from group 1. Macular traction was developed in 2 eyes of 1 patient in group 2. After the treatments, success in 122 eyes (96.8%) was obtained.

Conclusion: ROP can be controlled by convenient and effective treatment. Although conventional LPC is still the first treatment option for ROP, IVB alone or combination with LPC is a highly effective treatment option for zone 1 disease and APROP. IVB reduces the number of ROP treatments.

Keywords: Intravitreal bevacizumab; laser photocoagulation; retinopathy of prematurity.

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Address for correspondence: Selam Yekta Şendül, MD. Sisli Hamidiye Etfal Egitim ve Arastirma Hastanesi, Goz Hastaliklari Anabilim Dali, Istanbul, Turkey
Phone: +90 532 367 22 95 **E-mail:** sysendul@hotmail.com

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Retinopathy of prematurity (ROP) was first reported by Tery[1] in 1942, and it causes serious vision loss if not intervened in time.[2] The prevalence of blindness due to ROP is 1/50.000 worldwide. In recent years with the development of neonatal intensive care units, the incidence of ROP and the number of premature infants that can be survived increased.[3] The most important risk factors in the development of ROP are a low birth week and low birth weight.[4] In a multicenter study conducted in our country, the findings showed that preterms with fewer than 34 gestational weeks and birth weight less than 1700 grams should be screened for ROP.[5]

In the treatment of ROP, primarily ablation by laser photocoagulation (LFC) of the avascular retina is performed.[6] Thus, cells that produce vascular endothelial growth factor (VEGF) in the retina are destroyed. VEGF plays an important role in the progression of ROP.[7]

In the multicenter study of Early Treatment for Retinopathy of Prematurity (ETROP), pre-threshold disease was divided into two groups as high-risk (type 1 ROP) and low-risk (type 2 ROP), and it was reported that high-risk pre-threshold patients should be treated.[8]

However, the success rate of conventional LFC is lower in zone 1 than in zone 2 ROP cases, which causes peripheral visual field loss and marked myopia. Vitrectomy may be required in ROP that does not regress despite multiple applications.[9, 10]

Anti-VEGF agents are being used in the emergency treatment of acute ROP. Intravitreal bevacizumab (IVB) treatment was approved by the Food and Drug Administration in 2004 for metastatic colon cancer. IVB is not indicated in the treatment of ROP; IVB is used alone or in combination with LFC or vitrectomy.[11, 12]

This study aimed to evaluate the treatment models in premature infants treated for ROP, the effectiveness of treatment models, the number of their applications and the long-term results of treatment.

Methods

Premature babies who needed treatment for ROP and followed-up in the Neonatal Intensive Care Unit (NICU) of our hospital or external centers were retrospectively evaluated between January 2012 and January 2017. Informed consent was obtained from the first degree relatives of the patients included in this study. This study was approved by the Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital (Ethics Committee approval number: 1458/2017).

According to the criteria set by the American Academy of Ophthalmology, American Academy of Pediatrics and the American Association of Pediatric Ophthalmology and Strabismus, infants born at ≤30 gestational weeks or weighing less than 1500 grams at birth and infants born after 30 gestational weeks but whose clinical course was not stable underwent their fundus examinations 4 weeks after birth or when their gestational age reached 31-33 weeks.[13]

For dilatation of the pupil, one hour before eye examination tropicamide 0.5% (Tropamid, Bilim İlaç, Turkey) and 2.5% phenylephrine (Mydfrin, Alcon, USA) eye drops were used at 5 minute-intervals for three times. Topical anesthesia was provided with proparacaine hydrochloride (Alcaine, Alcon, USA). Priorly, optic disc and macula were examined with the aid of indirect ophthalmoscope and + 20D lens. Then, peripheral retina was examined with the aid of scleral indentation. All examinations were performed by two ophthalmologists (STD, DG). According to the criteria set by the International ROP Committee (International Classification of Retinopathy of Prematurity), the zones and stages of the cases were recorded.[14]

According to the ETROP study, patients with type 1 ROP and APROP were treated.[8] Patients were evaluated in three groups. Group 1: any stage in zone 1 together with plus disease, group 2: stage 2 or 3 diseases together with a plus disease in zone 2, group 3: APROP. As the first treatment, IVB (0.625 mg in 0.025 ml, injection at a distance of 1.5 mm from the limbus) was preferred in groups 1 and 3, and conventional 810 nm diode LFC (Iridex, Oculight SL, USA) was preferred in group 2. All avascular retina was ablated with conventional LFC (200-400 mW; 0.2-0.3 sec) at one and a half- spot diameter spacings. IVB treatment was applied to patients who could not be treated with LFC because the pupil could not be dilated or disease progression was detected despite LFC treatment. LFC+IVB treatment was applied to patients in whom LFC was thought to be ineffective or insufficient because of retinal or intravitreal bleeding. Treatments were performed under general anesthesia, sedation, or local anesthesia. Birth weights, birth weeks, treatment weeks, treatments were applied, and the number of cases were recorded. After treatment, topical antibiotic drops were applied for one week, and the patients were followed up weekly or two weeks apart depending on the severity of retinopathy. In case of recurrence in zone 1 and APROP, IVB was used if retinal vascularization still remained in zone 1, and LFC was applied if it advanced to zone 2. In case of recurrence in zone 2 ROP, LFC was used if the avascular retinal area was left, and IVB treatment was used if sufficient ablation was applied. Regression in plus disease, lack of development of macular traction, and retinal detachment were considered as successful treatment. Patients were followed up for at least two months after treatment.

Statistical Analysis

Intergroup rates of categorical variables were tested by chi-square analysis. Monte-Carlo simulation was applied when the required conditions were not met. Comparisons of nu-

merical variables in the independent binary group were performed by Kruskal-Wallis test since the condition of normal distribution was not provided. Subgroup analyzes were performed with the Mann- Whitney U test. Statistical significance level was accepted as $p<0.05$.

Results

A total of 1746 premature babies born before 38 weeks of gestation were examined between January 2012 and January 2017. Gender, gestational age, birth weight and distribution of the groups of patients treated for ROP are shown in Table 1. A total of 126 eyes of 65 (3.7%) premature infants, including 31 female and 34 male babies, were included in this study. Twelve (18.4%) patients were referred to our clinic from the NICU and 53 (81.6%) patients from the NICUs of external centers. The mean birth weight of the babies was 1159 (535-2200) grams, and the mean gestational age was 28.4±2.5 (24-34) weeks. Thirty eyes (26.1%) in group 1, 56 eyes in group 2 (56.3%), and 22 eyes (17.4%) in group 3 were examined.

Treatment models applied to the eyes are shown in Table 2. Ninety-four eyes (74.6%) received one treatment, 26 eyes (20.6%) 2 and 6 eyes (4.8%) three therapeutic applications. The distribution of the first treatment models applied to the groups is shown in Table 3. In the first treatment, LFC was applied to 64 eyes (50.8%), IVB to 57 (45.2%), and LFC+IVB to 5 eyes (4%). As the first treatment, 75.8% of group 1 and 95.5% of group three patients received IVB, and LFC was applied in 79.8% of group 2 patients. The need for re-treatment due to recurrence after the first treatment was shown in Table 4. Twenty-one (32.8%) of 64 eyes treated firstly with LFC and 11 (19.2%) of 57 eyes with IVB were re-treated due to development of recurrences. Recurrence did not develop in 5 eyes treated with LFC + IVB.

Second treatments applied because of the development of recurrences were evaluated in detail. Second treatments were administered to 4 eyes (12.1%) from group 1, to 16 eyes (22.5%) from group 2, and to 6 eyes (27.2%) from group 3. In group 1, LFC was applied to 3 eyes twice, firstly, IVB and then LFC were applied to 1 eye. In group 2, 12 eyes underwent LFC treatment twice, 2 eyes received firstly LFC, then IVB, and 2 eyes exposed to IVB followed by LFC. In group 3, 4 eyes received IVB followed by LFC and IVB was applied to 2 eyes twice. In group 1, second treatments were applied to one of 25 eyes (4%) that received IVB as the first treatment, 1 (4%) and 3 (37.5%) of 8 eyes that treated firstly with LFC were given second treatment. In group 2, second treatments were applied for 14 (25%) of 56 eyes treated with LFC in the first treatment and 2 (18.1%) of 11 eyes priorly treated with IVB. In group 3, 6 (28.5%) of 21 eyes that had been treated with IVB required a second treatment.

Table 1. Distribution of gender, birth week, birth weight of the patients treated with the indication of retinopathy of prematurity

Gender, n (%)	
Female	31 (47.7%)
Male	34 (52.3%)
Birth week	
Mean±SD (Min-max)	28.4±2.5 (24-34)
Birth weight	
Mean±SD (Min-max)	1159±444 (535-2200)
Groups, n (%)	
Group 1 (with 'plus' disease and any stage ROP in Zone 1)	33 (26.1%)
Group 2 (with 'plus' disease and stage 2 or 3 ROP in Zone 2)	71 (56.3%)
Group 3 (APROP)	%

ROP: Retinopathy of prematurity; APROP: Aggressive posterior retinopathy of prematurity, 'plus disease: increase in diameter and tortuosity of posterior retinal vessels.

Table 2. Distribution of the number of treatments in patients who underwent treatment for retinopathy of prematurity

Number of treatments applied for eyes	n	%
1	94	74.6
2	26	20.6
3	6	4.8

Table 3. Distribution of firstly applied treatments in each group

	Firstly applied treatments					
	LFC		IVB		LFC+IVB	
	n	%	n	%	n	%
Groups						
Group 1	8	24.2	25	75.8	0	0.0
Group 2	56	78.9	11	15.5	4	5.6
Group 3	0	0.0	21	95.5	1	4.5

LFC: laser photocoagulation; IVB: intravitreal bevacizumab.

Table 4. Requirement for re-treatments because of recurrences due developed after the first treatment

	First treatment		Recurrent treatments	
	n	%	n	%
Eye treatments				
LFC	64	50.8	21	32.8
İVB	57	45.2	11	19.2
LFC+İVB	5	4.0	-	-

LFC: laser photocoagulation; İVB: intravitreal bevacizumab.

Third treatments applied because of second recurrences of the disease were evaluated in detail. The third treatment was applied to two eyes of 1 patient from each group. In group 1, IVB was administered twice after LFC, in group 2, LFC + IVB was applied after 2 courses of LFC, in group 3, LFC + IVB was administered to the patient who had undergone a single course of IVB, and then LFC. Remissions developed after the third treatments in groups 1 and 2. Both cases were followed up for 24 months, and complete retinal maturation was observed. The patient in group 3 who could be followed up for only four months died due to respiratory distress. No retinal detachment or macular traction was detected during follow-up.

The first, second and third treatment weeks of the groups are shown in Table 5. The first treatments were applied at 35.2±2.2 weeks in group 1, 36.3±2.2 weeks in group 2 and 35.7±2.4 weeks in group 3. While there was a significant difference between the first treatment weeks between groups 1 and 2 (p=0.001), no significant difference was found between groups 1 and 3 and between groups 2 and 3 (p=0.068, and p=0.228, respectively). There was a significant positive correlation between birth week and birth weight and the first treatment week (p<0.001, p=0.017, respectively). There was no significant difference between the groups as for the second and third treatment weeks (p=0.588).

The patients were followed up for an average of 11 months (2-36 months). In group 1, one patient who received LFC treatment twice for his both eyes was referred to a technologically more advanced medical center because of the development of stage 4a retinal detachment. In group 2, macular traction developed in one patient who underwent LFC for his both eyes. Success was achieved in 122 eyes (96.8%) after the treatments were applied.

Discussion

ROP is one of the most important causes of blindness that can be prevented mostly by treatment in childhood. In recent years, the prevalence of ROP has been increasing, especially in developing countries, in line with the development of NICUs and the increase in the number of premature infants that can be survived.[3] In this study, we aimed to evaluate the treatment efficacy, recurrence rates and the treatments we use in case of recurrence, especially in infants receiving ROP.

Table 5. First, second and third treatment application weeks of the groups of patients treated for retinopathy of prematurity

Type 1 ROP	1. trtw Mean.±SD	2. trtw Mean±SD	3. trtw
Group 1	35.2±2.2	38.1±2.2	45
Group 2	36.3±2.2	39.5±2.8	44
Group 3	35.7±2.4	39.8±4.6	45
p	0.053	0.588	-

ROP: Retinopathy of prematurity; trtw: treatment week.

In the treatment of ROP, effective treatment modalities and indications for treatment in pre-threshold disease have been investigated. In the multicenter ETROP study, pre-threshold disease was divided into two groups as high-risk (type 1 ROP) and low-risk (type 2 ROP). Type 1 ROP disease was defined as zone 1 together with the plus disease with any stage; zone 1 with stage 3 without any plus disease, and zone 2 with stage 2 or 3. LFC treatment was applied to patients with type 1 ROP, and threshold disease and the results were compared. Since adverse retinal outcomes were less frequent, and visual acuity was better in type 1 ROP patients, relative to those with threshold disease, treatment of type 1 ROP patients was deemed to be necessary in various reports.[8] As a result of these studies, in the treatment of ROP, ablation of the avascular retina with trans-pupillary LFC is primarily applied within the scope of indication.

In our country, Günay et al.[15] evaluated the efficacy of LFC treatment in type 1 ROP, threshold disease and APROP, and reported that they achieved anatomic success in 84.7% of cases at the end of 1 year. Arvas et al.[16] from our country reported that 452 eyes with zone 1 type 1 ROP were treated with diode LFC and that in 98% of the cases that achieved a smooth, and flat macula. They also indicated that LFC in zone 1 ROP was an effective and reliable treatment. However, in the literature, the success rate of LFC is reportedly lower in patients in zone 1 than in patients in zone 2. In addition, it has been shown that patients with zone 1 ROP develop significant visual field loss due to LFC treatment.[17] Surgical treatment may be required in patients who do not regress despite multiple LFC treatments.[9, 10] As a result, new treatment options for ROP have started to be investigated.

Intravitreal bevacizumab (IVB) is currently used alone, together with LFC or vitrectomy in the treatment of ROP as an off-label treatment.[11, 12] IVB provides regression of the acute stage of the disease and saves time for the maintenance of retinal vascularization. Due to its large molecular weight of IVB, in animal studies, it has been shown that it enters into systemic circulation at a lesser extent when compared with other anti-VEGF drugs.[18] When LFC and IVB are applied in combination, its half-life is relatively long.[19, 20] The most important drawback of IVB is that there is no definite data on the safety of its use in the newborn. Another drawback is that although retinal vascular progression continues after IVB, the extreme retinal periphery can not be completely vascularized.[21] Moreover, the long-term outcomes of IVB

are not yet known. Hajrasouliha et al.[22] reported the development of bilateral tractional retinal detachment in a patient three years after IVB treatment.

In a multicenter, prospective, randomized BEAT-ROP study, IVB and LFC treatment in zone 1 and zone 2 posterior stage 3 ROP were compared. The need for re-treatment due to relapse up to 54 weeks after birth was evaluated. In zone 1 ROP; 6% of the IVB group and 42% of LFC group; In zone 2 ROP, 5% of the IVB group and 12% of LFC group of patients were re-treated. As a result, the findings showed that IVB was more effective than LFC in zone 1 ROP and that there was no difference between both treatment modalities in zone 2 posterior ROP.[23] In our country, Yetik et al.[24] evaluated the efficacy of IVB treatment in eyes with type 1 ROP, threshold disease, and APROP, and reported that regression was achieved with one to three injections in 95.4, 98.2, and 100% of the patients respectively. Nicoara et al.[25] compared IVB and LFC in APROP and reported that IVB was more effective than LFC.

In our study, recurrence rates after the first treatments were examined. In zone 1 ROP; recurrence after IVB was lower than LFC.

Although LFC treatment was mostly applied in zone 2 ROP and IVB treatment in zone 1 ROP and APROP, the recurrence rates after LFC treatment were higher than IVB treatment. Therefore, IVB treatment reduces the number of interventions to the eye compared to LFC treatment. LFC + IVB treatment can be applied in patients with zone 2 ROP whose pupils do not dilate due to neovascularization of iris and in zone 2 ROP patients in whom LFC is thought to be ineffective or insufficient as a result of the failure of LFC to reach the retina due to retinal or intra-vitreous hemorrhage.

In our study, recurrence rates after the first treatment were also examined. Although LFC treatment was mostly applied in zone 2 ROP and IVB treatment was mostly applied in zone 1 ROP and APROP, the recurrence rates after LFC treatment were higher relative to IVB treatment. Therefore, IVB treatment reduces the number of interventions to the eye compared to LFC treatment. LFC + IVB treatment can be applied in patients with zone 2 ROP whose pupils do not dilate due to neovascularization of iris, and in whom LFC is thought to be ineffective or insufficient as a result of failure to reach the retina due to retinal or intra-vitreous hemorrhage.

In our study, we also comparatively evaluated the type of treatment we applied in case of recurrence between the groups. In case of recurrence, after IVB treatment in zone 1 and APROP, the second treatment option was decided according to retinal vascularization. If retinal vascularization remained in zone 1, IVB was applied again, and if it progressed to zone 2, then, LFC treatment was applied. IVB treatment was applied to eyes whose pupils did not dilate due to neovascularization of iris. In zone 2 ROP, in case of recurrence after LFC treatment, if there was still avascular retinal area left, LFC was repeated, and IVB treatment was applied if sufficient ablation was applied. Thus, in case of recurrent retinal vascularization, the second treatment option should be decided according to the presence of retinal vascularization in case of recurrence in zone 1 and APROP after IVB, and to the width of the avascular retinal area remaining after LFC in zone 2 ROP.

In our study, we also comparatively evaluated the treatment weeks between the groups. The findings showed that the need for early ROP treatment increased as the gestational week decreased. In addition, the first treatment was applied earlier in eyes with zone 1 ROP compared to eyes with zone 2 ROP. This condition may be related to the width of the avascular retinal area. The larger the avascular area, the greater is the amount of secreted VEGF, and therefore, early treatment may be required.

Conclusion

In conclusion, ROP can be controlled with appropriate, timely and effective treatment. Although conventional LFC is still the first treatment option in ROP, IVB is an effective treatment option in zone 1 disease and APROP alone or in combination with LFC. IVB reduces the number of eye interventions in the treatment of ROP. In case of recurrence, the treatment option should be decided according to the retinal vascularization in zone 1 disease and APROP, and in zone 2 ROP, it should be decided according to the width of the avascular retinal area remaining after LFC.

Disclosures

Ethics Committee Approval: This study was approved by the Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital (Ethics Committee approval number: 1458/2017).

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