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Turkish Neonatal and Turkish Ophthalmology Societies consensus guideline on the retinopathy of prematurity

Türk Neonatoloji Derneği ve Türk Oftalmoloji Derneği prematüre retinopatisi uzlaşı rehberi

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Abstract

Retinopathy of prematurity is a pathophysiological condition that occurs in relation to abnormal proliferation in the retinal vessels in premature babies. Its exact pathogenesis is not known. In Turkey, the increased chance of survival in premature babies with much younger gestational age and much lower birth weight in parallel with the developments in neonatal care causes retinopathy of prematurity, which has led to vision problems and blindness to emerge as a more frequent problem. Early diagnosis and timely and appropriate treatment of retinopathy of prematurity contributes to the developmental process and increases the quality of life by preventing vision loss. It should be kept in mind that retinopathy of prematurity may also lead to serious medicolegal problems.

Keywords: Oxygen, prematurity, retinopathy, newborn

Öz

Prematüre retinopatisi erken doğan bebeklerde retinal damarların anormal proliferasyonuna bağlı oluşan ve patogenezi tam olarak bilinmeyen fizyopatolojik bir durumdur. Ülkemizde yenidoğan bakımındaki gelişmelere paralel olarak gebelik yaşı ve doğum ağırlığı çok daha küçük prematüre bebeklerin yaşama şanslarının artması görme sorunlarına ve körlüğe neden olabilen prematüre retinopatisinin daha sık bir sorun olarak karşımıza çıkmasına neden olmaktadır. Prematüre retinopatisinin erken tanınması, zamanında ve uygun şekilde tedavisi görme kaybını engelleyerek çocuğun gelişimsel sürecine katkıda bulunmakta ve yaşam kalitesini artırmaktadır. Prematüre retinopatisinin ciddi medikolegal sorunlara da neden olabileceği unutulmamalıdır.

Anahtar sözcükler: Oksijen, prematürite, retinopati, yenidoğan

Introduction

The objective of this national guideline on the diagnosis and treatment of retinopathy of prematurity (ROP) is to propose recommendations related to the diagnosis, treatment, follow-up, and prevention of ROP in preterm babies who are followed up in neonatal intensive care units (NICUs) and carry risk in terms of ROP, in light of scientific data and the conditions of our country.

1. Epidemiology

The incidence of retinopathy of prematurity varies according to the levels of development of countries and the characteristics of NICUs. In developed countries, ROP is a problem predominantly for preterms born befor the gestational age of 28 weeks, whereas it has been reported that severe ROP develops up to the 34th week in developing countries.

In a multi-center study conducted by the Turkish Neonatal Society in 2014, the overall incidence of ROP was found as 42% and the incidence of severe ROP was 8.2% in very-low-birth- weight preterm babies. In this study, t the incidence of severe ROP was 0.4% in babies with a gestational age over 32 weeks. Severe ROP was found in

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20 babies with a gestational age (GA) above 32 weeks, in 41 babies with a birth weight (BW) of >1500 g and in three babies with a BW of >2000 g.

The results of this study showed that advanced stage ROP requiring treatment developed in more mature babies in our country compared with developed countries (1).

2. Risk factors

Although numerous etiologic factors have been considered in the development of retinopathy of prematurity, the best-known risk factors include low BW and low GA. It is known that the incidence of ROP markedly increases especially in babies who are born with a BW below 1000 g and a gestational age less than 28 weeks (Table 1) (1-4).

3. Pathogenesis

The retina is avascular up to the 16th week of gestation after fecondation. The hyaloid artery supplies the lens and anterior segment, which develop in this period. The developing retina is supplied by the choroid vessels by way of diffusion, because the hyaloid artery initially does not have any sub-branches. Development of the retinal vessels in the fetus begins in the 15-18th gestational week. The retinal vessels develop from the optic disc to the periphery and vascularization is completed at about the 36th week in the nasal retina and in the 40th week in the temporal retina. Therefore, the retina is not completely vascularized at the time of birth in preterm babies and there is a peripheral avascular zone with varying width depending on the GA at the time of birth. Completion of vascularization may be delayed up to the postmenstrual age (PMA) of 48-52nd week. Regulation of the expression of vascular endothelial growth factor (VEGF) and other cytokines appear to contribute to both normal retinal vessel growth. Insulin-like growth factor-1 (IGF-1) supports normal retinal vascular growth and interacts with VEGF (5).

Although the pathogenesis of retinopathy of prematurity is not known exactly, it is thought that it develops in two stages. Retinal revascularization, which begins in the intrauterine setting, pauses because of any damaging effect in the preterm baby. Hypoxia or hyperoxia with free radical formation, asphyxia, hypothermia, acidosis, and hypotension are among the possible causes of initial injury (2).

In the early phase of retinopathy of prematurity (Phase I), dysregulation of expression of VEGF,erythropoietin and other cytokines due to hyperoxia or insult, low serum concentrations of IGF-1, and inadequate postnatal growth inhibit normal vascular development (2, 4).

Table 1. The principal risk factors for development of retinopathy of prematurity

Low gestational age and low birth weight
Duration and concentration of oxygen treatment
Hemodynamically significant cardiorespiratory problems
Hyperoxia/hypoxia, hypercapnia/hypocapnia
Asphyxia, hypothermia, metabolic acidosis
Mechanical ventilation lasting more than one week
Bronchopulmonary dysplasia
Sepsis/meningitis, systemic fungal infections
Intracranial hemorrhage
Number of blood transfusions, exhange transfusion
Early use of erythropoetin for treatment of anemia of prematurity
Multiple pregnancy

The retina continues to pursue its development, but its oxygen need is not met because vascularization is impaired and it becomes hypoxic. Exposure to hypoxia in the retina initiates the 2nd phase. Hypoxia triggers an increase in the levels of the mediators including VEGF, erythropoietin and IGF-1 levels rise during maturation reaching a critical level and neovascularization ensues. Neovascularization is seen in the vascular-avascular retinal border. The newly formed vessels may lead to clusters inside the retina and a rapidly thickening ridge tissue may be formed. Neovascularization may lead to leakage and edema and retinal detachment, which results in loss of vision (4-6).

4. Classification

The classification of the disease according to the International Classification of Retinopathy of Prematurity (ICROP) is presented below (5, 7, 8).

4.1. Location (Zone): The retina is divided into three regions with the optic nerve being the center in order to indicate the localization of the disease.

Zone 1: Central zone at the posterior pole of the eye. The circular area with a radius twice the distance between the optic nerve and macula

Zone 2: The circular area with a radius equal to the distance between the optic nerve and nasal ora serrata

Zone 3: The crescent-shaped region in the temporal area

4.2. Stage (degree of vascular proliferation): The disease is divided into 5 stages considering the degree of vascular proliferation.

Stage 1: The demarcation line separating the vascular and avascular retina;

Stage 2: Ridge; protuberant structure;
Stage 3: Initiation of extraretinal fibrovascular proliferation in the ridge;
Stage 4A: Partial retinal detachment (macula is not involved);
Stage 4B: Partial retinal detachment (macula is involved);
Stage 5: Total retinal detachment.

4.3. Extent Expansion: The retinal surface is divided into sectors of 30º similar to a clock dial. In this way, it can be specified how many clock dial segments the disease has expanded. The stage of the disease may show variance between sectors.

4.4. Plus disease: Plus disease is defined as increased tortuosity in the arterioles and dilatation of the veins in the posterior pole of the retina. Presence of plus disease is an indication of the severity of ROP and may be associated with opacity in the vitreus, dilatation in the vessels of the iris, and decreased pupilla reactions.

4.5. Preplus disease: Posterior pole tortuosity and dilatation that are not sufficiently abnormal to reach the criteria of plus disease.

4.6. Threshold disease: Threshold disease is defined as involvement of 5 consecutive clock segments or 8 non-consecutive clock segements in the presence of stage 3 and plus disease in zone I or zone II.

4.7. Pretreshold disease:
Any stage of ROP in the absence of threshold disease in zone I.
Stage 2 ROP and plus disease in zone II.
Stage 3 ROP in zone II.
Stage 3 Rop and plus disease in zone II with less sector involvement compared with threshold disease.

4.8. High-risk prethreshold disease: "Threshold ROP" is a term that was previously used to describe the threshold at which treatment was needed. However, treatment is now initiated when the infant develops high-risk prethreshold ROP, also called "type I ROP." Type I ROP is defined as any of the following
Plus disease at any stage in zone I.
Stage 3 ROP in zone I (in the presence or absence of plus disease).
Stage 2 or stage 3 ROP and plus disease in zone II.

Severe ROP is found in conditions where stage 3 and above ROP or plus disease is present. Aggresive posterior ROP (APROP) is a severe form of ROP that progresses rapidly. If it is not treated, it rapidly progresses to stage 4 and 5. This picture was previously defined as 'rush disease" and it was redefined as APROP in 2005. In these eyes, plus disease is prominent in 4 clock segments at a level that is inproportionate to the disease in the peripheral area. Although zone I or posterior zone II disease is present, the borders cannot be differentiated exactly. It may be difficult to determine the stage.

Flat neovascularization may be present in the borders and the diagnosis may be missed because a protuberant surface is absent. Another characteristic of this disease is that it may progress to stage 4-5 without pursuing the standard path from stage 1 to stage 3. When a diagnosis of aggressive posterior ROP is made, medical interventions should be urgently initiated without making assessment for classification in terms of vascular proliferation stages.

5. Clinical prognosis

The prognosis of retinopathy of prematurity is associated with the PMA and the location of the disease rather than postnatal age. The onset may occur in the postmenstrual age 30-32 weeks, but typically occurs in the 34th week. It progresses irregularly until the 40-45th gestational age and mostly recovers spontaneously. ROP develops in two-thirds of babies born with a birth weight of ≤1250 g and medical intervention is required because of severe disease in approximately 6% of these babies (9-12).

6. Ophthalmologic follow-up of preterm babies

6.1. Diagnosis and screening

According to the 2013 recommendations of the American Academy of Pediatrics and American Academy of Ophthalmology, all babies born with a BW of ≤1500 g and/or a GA of ≤30 weeks, and babies born with a GA above 30 weeks and a BW of 1500-2000 g who have clinical problems and need cardiopulmonary support should be screened (13).

Our recommendation for our country is as follows: All preterm babies with a GA of ≤32 weeks or a BW of ≤1500 g, and babies born with a GA of >32 weeks or a BW of >1500 g who have undergone cardiopulmonary support treatment or are considered to "carry a risk in terms of development of ROP by the physician monitoring the baby" should be screened. The first ophthamologic examination is performed in the PMA of the 30-31st week in babies born with a GA below 27 weeks and in the postnatal fourth week in babies born with a GA of ≥ 27 weeks (Table 2) (13). The postmenstrual age (PMA) is used in the follow-up visit schedule for retinopathy of prematurity (gestational age+chronologic age) (14).

Table 2. Time of the first follow-up visit for retinopathy of prematurity by gestational age (13)

Gestational age (weeks)	The time of the first follow-up visit (weeks)	
	Postmenstrual	Chronologic
22[a]	31	9
23[a]	31	8
24[a]	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32[b]	36	4

[a]The first follow-up visit can be performed when the postnatal sixth week is completed without waiting for the postmenstrual 31 week in babies born with a gestational age below 25 weeks

[b]The first follow-up visit is performed when the postnatal fourth week is completed in babies born with a gestational age above 32 weeks

6.2. Examination and points to consider

Retinal examination is performed by an ophthalmologist who is competent and qualified in the area of ROP with binocular indirect ophthalmoscope using 20 and 28 diopter lens after placing an eyelid speculum. The baby should be in the supine position during the examination. In the period during which the baby is hospitalized, it is ideal to perform ophthalmologic examinations inside the neonatal unit and in the accompaniment of intensive care physicians with monitorization of the patient.

Families are informed about ROP examination and monitoring, verbally and in writing. Consent/approval should be obtained from families before the first examination. If the family does not give consent, approval should be obtained from the court for a legal act based on the baby's high right to live. The date of consultation for examination of retinopathy of prematurity should be specified in the consultation paper. The name of the ophthalmologist who performed the examination for retinopathy of prematurity and the examination date should be included in the documents. The examination notes of the ophthalmologist should include detailed information related to zone, stage, extension, and presence of plus disease, treatment plan, and the date of the next follow-up examination.

The pupil should be dilated to visualize the retina and vitreus. Adequate dilatation of the pupil enables examination of the peripheral retina and facilitates staging of ROP (15, 16). The mydriasis procedure is initiated 1 hour before examination. Our recommendation is to dilate the pupil using one drop of 2.5% phenylephrine and 0.5% tropicamide 2-3 times with an interval of 5 minutes. The 45-60th minute after the final drop is generally the time when the best pupil dilatation is obtained.

When the pupil is not dilated well, mydriatic drops are administered again and this may lead to more adverse effects. However, it should be kept in mind that pupils of patients with severe ROP may not dilate well.

Manipulation of the eye and the drops used may lead to bradicardia, tachycardia, cardiac arrythmia, apnea, desaturation, hypertension, vomiting, gastric residue, transient paralytic ileus, and rarely mortality (15, 16).

Mydriatic drops may be absorbed in the skin around the eye, cornea, conjunctiva, nasal mucosa, and nasolacrimal duct. Reduction of absorption decreases the risk of adverse effects. The following precautions can be applied to decrease the risk of adverse effects caused by the eye drops: application of small drops, wiping away drug leaking around the eye or closing the eyelid after application of the drop, decreasing systemic absorption by applying pressure on the lacrimal sac, internal canthus for 2 minutes after application of the drop, and paying attention to performing a timely examination to prevent readministration of the drug.

ROP examinations and especially use of a speculum is a painful procedure. It is important to use topical anesthesia and to provide sedation, if possible (17-19). Our recommendation for topical anesthesia is as follows: One drop of proparacaine hydrochloride (0.5%) is applied in both eyes 3-5 seconds before the examination. Its action lasts for about 15-20 minutes.

It is recommended that the baby should be held by a nurse such that the head and arms are fixed, the hands and feet should be gently put in the flexion posture or the baby should be loosely swaddled. Giving a pacifier, breastmilk or oral sucrose during and after examination is helpful in reducing pain.

Eye examinations may lead to infectious conjonctivitis and systemic infections. Ophthalmologists should adequately wash their hands before each examintion and adhere to all hygenic rules. A sterile eyelid speculum and sclera indentor is used for each patient. An autoclave

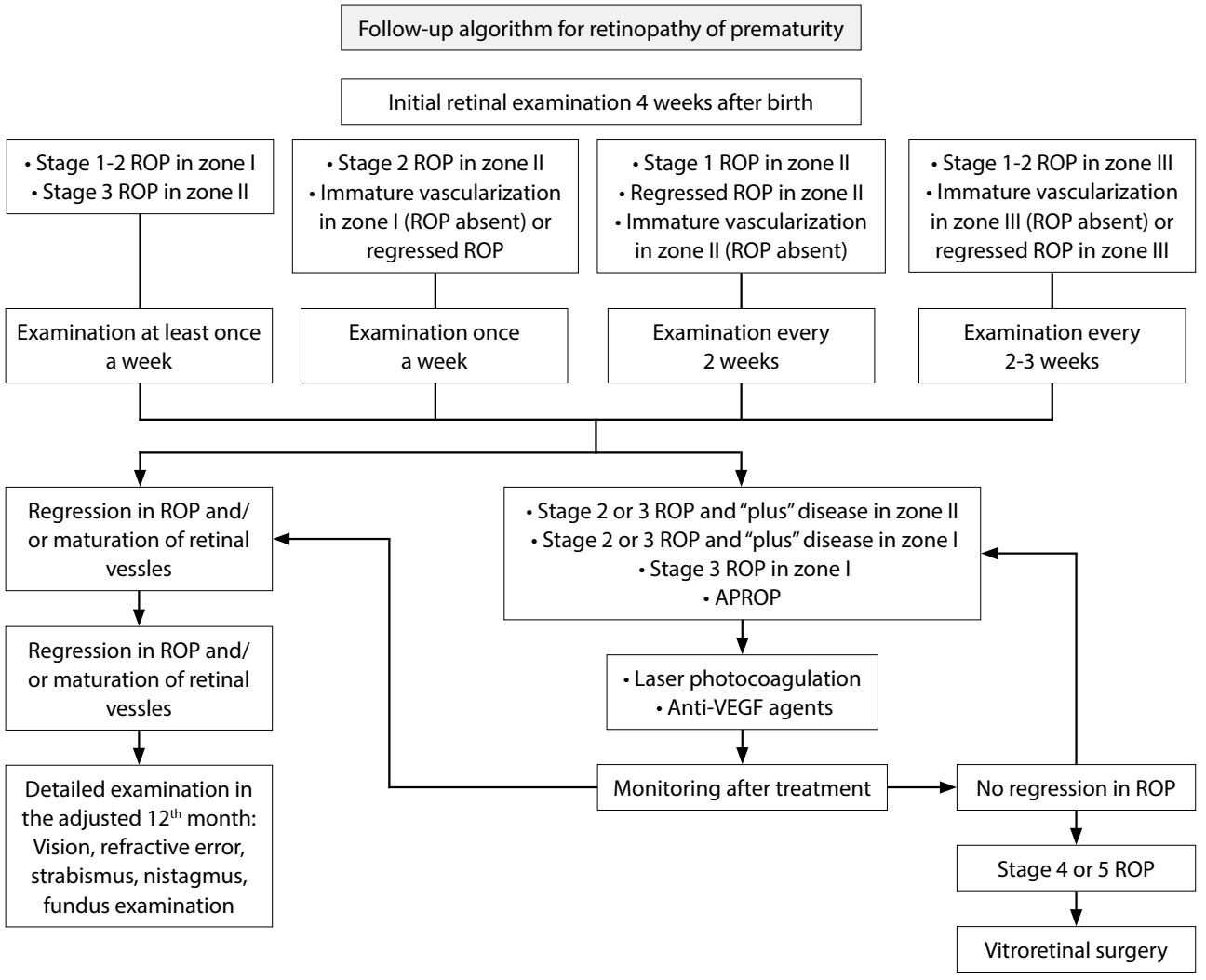

Figure 1. Follow-up algorithm for retinopathy of prematurity
ROP: retinopathy of prematurity

should be used for disinfection of the equipment used during the examination (20).

7. Follow-up

The follow-up schedule of preterm babies in terms of ROP is framed according to the findings on the initial examination. If development of retinopathy is found on the initial examination, the follow-up schedule is formed according to the disease severity and progression. If retinal vascularization is in zone III, examination is repeated every 2-3 weeks, if it is in zone II, examinations are repeated at least every 2 weeks. If it is found in zone I, examinations are performed at least once a week depending on the presence of progression. Screening examinations continue until ROP regresses or full retinal vascularization is completed (21, 22).

Devices that enable digital retinal imaging have recently become available. The decision for termination of follow-up and treatment decisions should be made according to the result of examination performed with a binocular ophthalmoscope. Further studies are needed to evaluate the sensitivity, advantages, and use of devices that take and record digital photos (13, 15). The follow-up algorithm for retinopathy of prematurity is shown in Figure 1. This algorithm is advisory. The physician monitoring the baby will specify the follow-up frequency according to the findings of the disease.

8. Termination of screening examinations

In babies in whom retinopathy of prematurity has not been found, the risk of development of sight-threatening ROP is very low after the retinal vessels reach zone III. The decision for termination of follow-up examinations should be made when retinal vascularization is completed, though it is not easy to determine if the retinal vessels have reached zone III. Screening examinations

can be terminated in the conditions specified below (14):

- Full retinal vascularization (this criterion is especially more important in patients who receive anti-VEGF agent);
- Absence of zone I or II ROP on previous examination and reaching of retinal vascularization to zone III (if the ophthalmologist is suspicious about zone or if the baby is aged below the PMA of 35 weeks, reexamination is recommended);
- Babies in whom prethreshold or worse ROP has not been found on previous screening examinations and who have reached the PMA of 45 weeks;
- ROP: absence of abnormal vascular tissue which might carry a risk for reactivation or progression.

9. Treatment

9.1. Retinal ablative treatment

Laser photocoagulation is the standard treatment method. The objective in treatment is ablation of the avascular peripheral retinal areas. This procedure is performed using diode laser photocoagulation. Laser treatment is applied in all avascular areas in front of the vessels where ROP has developed rather than on these vessels. Retinal ablation treatment is indicated in 'threshold disease' and high-risk 'prethreshold disese' (13, 23).

The criteria for laser photocoagulation in retinopathy of prematurity have been specified by the Early Treatment for Retinopathy of Prematurity (ETROP) study group. In these criteria, the findings of high-risk prethreshold ROP (type I ROP) have also been considered (13, 24). It has been reported that early treatment increases visual acuity and reduces negative structural outcomes. Medical interventions should be initiated as soon as possible in cases of aggressive posterior ROP and in 48-72 hours in non-aggressive cases (25). The following conditions require treatment according to the Early Treatment for Retinopathy of Prematurity criteria:

- Stage 1 or 2 ROP and plus disease in zone I;
- Stage 3 ROP in zone I;
- Stage 2 or 3 ROP and plus disease in zone II.

Pain, apnea, bradycardia, chemosis, intravitreal hemorrhage, infection, iris and lens tears, cataract, posterior synechia, glaucoma, decrease in visual acuity, and frequently reduction in visual field may be observed after laser treatment. Cataracts are observed less frequently in diode laser treatment compared with argon laser treatment. Rarely, anterior segment ischemia may also develop as a result of intensive laser treatment applied especially in cases of APROP. This complication is a severe problem that may lead to loss of vision (26).

Despite laser treatment, retinal detachment may develop and progression to stage 4 may occur in some patients. The risk of retinal detachment increases in conditions where vitreus hemorrhage is present or white fibrous structures are formed in the vitreus (27).

9.2. Anti-VEGF agents

Bevacizumab (Avastin®), ranibizumab (Lucentis®) and aflibercept (Eylea®) are anti-VEGF agents and constitute an alternative method in ROP treatment. They are administered as intravitreal injection. Anti-VEGF agents are used in many retinal vascular pathologies in adults such as macular degeneration, diabetic retinopathy, retinal vein obstructions, and in the treatment of ROP in preterms (28, 29).

Laser photocoagulation is the gold standard in the treatment of ROP. However, anti-VEGF agents have some advantages including easier administration, rapid response, absence of narrowing in the visual field, and opportunity of use in conditions where the cornea is opaque, the vitreus is cloudy, and the pupil is not dilated (30-32). Their potential disadvantages include transient reduction in serum VEGF levels and injury in the brain, lung, and kidneys (33, 34). In addition, they may disrupt normal retinal vascularization. The lowest effective dose is not known, but generally half of the dose used in adults is administered (bevacizumab: 0.675 mg / 0.025 mL, ranibizumab: 0.25 mg / 0.025 mL).

In a multi-center study in which bevacizumab and laser photocoagulation were compared, it was reported that recurrence and structural abnormalities (retinal detachment, macular ectopia) occured with a lower rate at the PMA of 54 weeks following the use of bevacizumab in the treatment of stage 3 ROP in zone I or posterior zone II ROP (30).

Unresponsiveness occurs about 2-3 weeks after laser treatment. Late recurrence has been reported after bevacizumab treatment. Therefore, it has been reported that follow-up should be pursued for a longer term after bevacizumab treatment (35, 36). Peripheral retinal vascularization decelerates to a great extent in babies in whom anti-VEGF has been administered. In these babies, that follow-up until peripheral vascularization is completed is important and may last up to the age of 2-3 years. Follow-up should not be neglected because potential activations have been reported in the long term. Examination under general anesthesia may be necessary because peripheral retinal examination may be difficult in a mature baby. It may be an appropriate approach to finalize long-term follow-up by applying laser in the re-

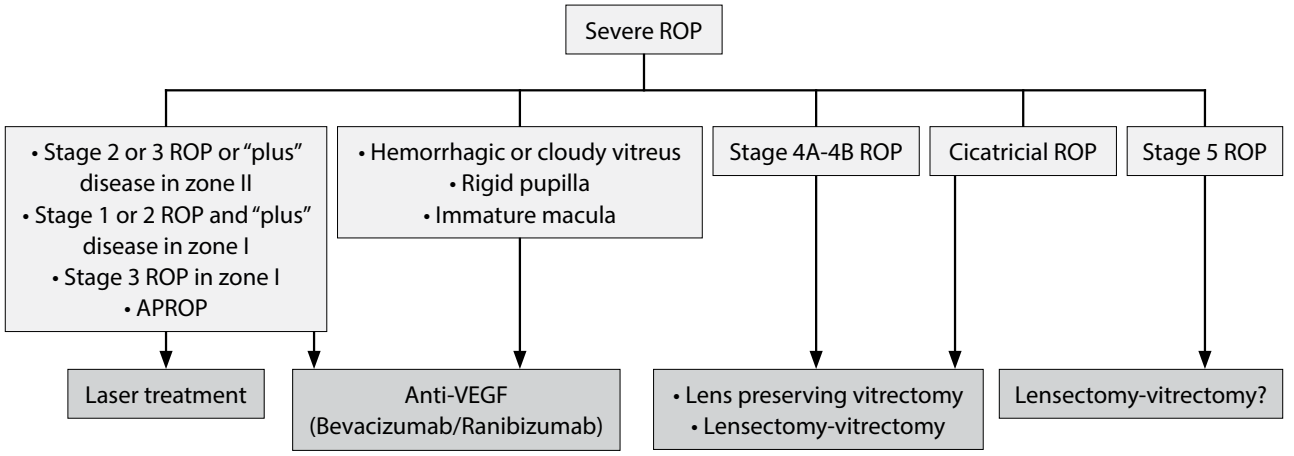

Figure 2. Treatment approach in retinopathy of prematurity

APROP: aggressive posterior ROP; ROP: retinopathy of prematurity; VEGF: vascular endothelial growth factor

maining avascular areas after the disease has reached the anterior zone 2 (37).

Despite all these unknown points related to Anti-VEGFs, the clinical conditions in which use of these agents may be considered primarily are listed below:

- ROP in zone I or posterior zone II;
- Presence of aggressive posterior ROP;
- Conditions where the macula has not yet been vascularized (immature macula): to avoid laser treatment of the macula;
- Presence of conditions that hinder visualization of the retina: Inadequate pupil dilatation, corneal opacity, cloudy/hemorrhagic vitreus;
- Babies whose general states are too problematic to tolerate laser treatment

The American Academy of Pediatrics emphasized that bevacizumab may be considered in zone I stage 3 ROP + plus disease, but further studies should be conducted to determine the dose, optimal timing, safety and efficiency (13). In addition, bevacizumab usage in ROP treatment has not been approved by the United States Food and Drug Administration (FDA) and the Republic of Turkish Ministry of Health. Written consent must be obtained from families before treatment.

9.3. Surgical intervention

If retinopathy of prematurity advances to subtotal or total detachment (stage 4, stage 5), surgical interventions are performed to prevent retinal detachment and preserve vision.

Vitrectomy is excision of the fibrovascular tissue, which leads to traction of the retina following surgical removal of the vitreus. It is a technique that provides relief and resettlement of the retina. In cases where the retina has drifted too anteriorly, the lens may sometimes be sacrificed to enable retinal relief. Even if treatment is successful, poor vision or blindness may develop in many patients. Although better outcomes can be obtained in terms of both anatomy and visual function in stage 4A, success rates are very low in stage 4B or stage 5 (38, 39).

Surgery is mostly not recommended, especially in stage 5. However, a chance could be given at least to one eye in bilateral involvement and in very early stage 5. In a small number of stage 5 patients, it is possible to achieve ambulatory vision (40). Our recommendations for the treatment approach are shown in Figure 2.

9.4. Treatment setting

It is important to protect the baby from hypothermia and to monitor vital signs during laser treatment. Treatment can be performed under operating room conditions or in a separate and dark setting inside the NICU. Vitroretinal surgery is performed under operating room conditions, but anti-VEGF agents can be administered in appropriate settings prepared for injection. Monitorization should be continued during and after the procedures.

9.5. Anesthesia

Laser treatment can be performed in the NICU under the guidance of a neonatologist by implementing intravenous sedative analgesia if operating room conditions are not available. Topical anesthesia is not recommended because it does not provide adequate analgesia by itself (15, 41).

9.6. Follow-up after treatment

The first follow-up visit following treatment should be conducted within 3-7 days and repeated once a week until the disease shows regression. If there is no regres-

sion in ROP after treatment, incomplete areas where the laser could not be applied adequately are suspected or new avascular areas emerging as a result of regression of neovascularization are present, laser treatment can be repeated in a time period that will be decided by an ophthalmologist.

Patients who develop ROP should be examined periodically following discharge in terms of potential ophthalmologic problems regardless of having received laser treatment, and patients with severe ROP or those who have received treatment should be followed up at least up to the age of five years (13, 15).

9.7. Use of eye drops after treatment

Use of prophylactic steroid and mydriatic drops up to 7 days following laser treatment may be recommended to prevent the development of hyphema, posterior synechiae, and transient cataracts. Prophylactic antibiotic drops may be used at a dose of 3x1 up to one week following intravitreal anti-VEGF injection. Drops containing topical steroids, antibiotics, and cycloplegic agents should be used for time periods specified by surgeons (up to 4-6 weeks) following vitreoretinal surgery (15).

10. Prognosis

Prognosis of ROP is variable; onset in zone I, rapidly progressing disease, plus disease, and retinal detachment are indicators of poor prognosis. Onset in zone II and slowly-progressing disease generally result in complete recovery or partial retinal scar. Onset in zone III indicates the best prognosis and complete recovery occurs (10).

In a study in which 760 patients were followed up, it was found that the mean time for ROP regression was PM 38-44th weeks in 90% of patients. It was reported that prognosis was very good in 99% of patients in whom ROP regressed from zone II to zone III and partial or total retinal detachment was not present in conditions limited to zone III (11).

The prevalence of blindness and severe visual impairment related to retinopathy of prematurity is not known exactly. However, ophthalmologic problems develop in 6-10 years in 55% of patients in whom regression is observed (12). Myopia, strabismus, nystagmus, and amblyopia occur more commonly in babies who develop mild ROP (stage 1 disease or stage 2 disase not accompanied by plus disease) compared with term babies (10). Ophthalmic morbidities including galucoma, retinal detachment, nistagmus, cataract, optic atrophy, macular problems, microcornea, phthisis bulbi, and refractive errors may develop in patients who develop severe ROP and/or who receive treatment (42).

All preterm babies are followed up in terms of vision, refractive errors, and strabismus up to the preschool period. The follow-up scheme to be conducted after discharge should be described in detail and it should be recorded in the patient's file that the family has been informed.

11. Prevention

Although the development of ROP is multifactorial, one of the main risk factors is oxygen treatment and its duration. The most important preventive factors in terms of decreasing the frequency and development of ROP include avoiding repetetive hypoxia-hyperoxia periods and measurement and limitation of the level of oxygen adminestered.

There are randomized, controlled studies with high-level evidence addressing the question at which level oxygen saturations should be kept from birth to the PM 36-40th week as long as additional oxygen need continues in preterm babies with a gestational age below 28 weeks. In the Benefits of Oxygen Saturation Targeting Trial (BOOST II), no difference could be found between the groups in which low and high oxygen saturation was targeted in terms of mortality and the frequency of major neurologic disorders, according to adjusted follow-up results. In the Canadian Oxygen Trial (COT), no difference was found between the groups in which low (85-89%) and high (91-95%) oxygen saturation was targeted, in terms of development of ROP. In the study of the SUPPORT group, an increase in mortality was reported, although severe ROP was reduced in the group in which low oxygen was targeted. In preterm babies who need additional oxygen, it is recommended that the target oxygen saturation should be 90-95% (43-46).

The effects of antioxidant therapies including vitamin E and D-penicillamine and applications including reducing exposure to light on development of ROP have been investigated. It has been reported that use of vitamin E reduced the severity of ROP, but increased the risk of sepsis and necrotizing enterocolitis. It was found that D-penicillamine and reducing exposure to light did not decrease the frequency of ROP. In light of the information obtained about the pathophysiology of ROP, new preventive and therapeutic methods are being investigated. Studies related to the use of IGF-1 replacement, propranolol, and inositol with the objective of reducing the development of severe ROP are continuing (47-50).

In conclusion, good antenatal care, appropriate delivery room management, good clinical applications during the

hospitalization period in the NICU, providing appropriate postnatal weight gain, and raising awareness among nurses and physicians about measurement, monitoring, and controlling the level of oxygen administered are important in decreasing the prevalence of ROP.

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