Chapter 6

Indirect Diode Laser in the Treatment of Retinopathy of Prematurity

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79828

Abstract

Retinopathy of prematurity (ROP) is a largely preventable cause of visual impairment in children. The golden standard of treatment in ROP is the laser photocoagulation of the non-vascularized retina. The most vulnerable period when ROP is at high risk of rapid progression is comprised between 34 and 35 weeks postconceptional age (PCA) and 36–37 weeks PCA. We carried out a retrospective study in which we included all the ROP cases treated by indirect diode laser photocoagulation between January 1, 2006, and December 31, 2017, totalizing 110 premature infants of which, 60 were males (54.54%) and 50, females (45.45%). Mean gestational age (GA) was 28.30 weeks and mean birth weight (BW) was 1121 grams in our series. Of the 110 preterm infants, 74 were the result of single pregnancies (67.27%) and 36 of multiple pregnancies (32.72%). At the moment of treatment, the mean postnatal age (PNA) was 8.38 weeks and the mean PCA, 37.02 weeks. ROP regressed after laser treatment in 185 eyes (88.09%). Statistical tests proved that regression rate was significantly worse in aggressive posterior ROP as compared with stage 3 zone 2 and stage 3 zone 1 ROP (odds ratio = 13.53, relative risk = 7.79, $P < .001$).

Keywords: retinopathy of prematurity, pediatric blindness, indirect diode laser, ROP treatment, ROP outcome

1. Introduction

Retinopathy of prematurity (ROP) can be a major cause of pediatric blindness worldwide if not diagnosed and treated promptly [1]. Visual loss in ROP is due to the complications related to retinal ischemia: retinal neovascularization, vitreous hemorrhage and finally total retinal detachment. Fortunately, ROP is a largely preventable cause of visual impairment in children. Despite the fact that in recent years, intravitreal anti-VEGF agents proved their efficacy and safety in the

management of ROP, the golden standard of treatment in ROP remains the laser photocoagulation of the non-vascularized retina [1].

2. Indirect diode laser photocoagulation in the treatment of ROP

In order to understand the rationale of laser treatment in ROP and its mechanism of action, the pathogenesis of ROP is summarized, as well as its classification and indications for treatment. Practical considerations on indirect diode laser photocoagulation for ROP are presented subsequently.

2.1. Pathogenesis of ROP

Vasculogenesis and *angiogenesis* are two distinct terms that need to be explained. In the vasculogenesis process, the origin of blood vessels is represented by the endothelial progenitor cells that coalesce and form lumen and vasculogenic networks. In the angiogenesis process, the new vessels form from the existing ones by vascular sprouting [2].

ROP is a biphasic disease directly related to the saturation of oxygen, which is administered in order to maintain the prematurely born vital functions. Phase 1 (between 22 and 30 weeks PCA) is characterized by relative hyperoxia and decreased vascular endothelial growth factors (VEGF) levels. The consequence of this situation is delayed vessel formation. Phase 2 (between 31 and 44 weeks PCA) is defined by relative hypoxia and increased VEGF levels, having as consequence uncontrolled vessel growth.

The cause of ROP is the non-development of retinal vessels with subsequent retinal ischemia and new vessel proliferation [2].

2.2. ROP classification

Screening for ROP is essential for reducing the blindness rate related to this disease [3]. It should be made by indirect ophthalmoscopy by specially trained ophthalmologists according to criteria which are specific to each country/region.

In classifying ROP, the following criteria are used: zone, stage and the presence/absence of "plus" disease. The retina is divided into three zones and 12 clock hours. Zone 1 corresponds to a circle having the radius equal to the double distance between the optic disc and the fovea. Zone 2 describes a circle with the radius that equals the distance between the optic disc and the nasal ora serrata. Zone 3 is the remaining "crescent" of retina in the temporal area [3, 4].

Stages are defined according to the modifications at the limit between the vascularized and non-vascularized retina. Stage 0 reflects no modification at this level, but the retinal vascularization is not yet completed. In stage 1, a demarcation line (within the retinal plane) is identified at this site. In stage 2, there is a non-vascularized, white ridge (elevated from the retinal plane) at the limit between the two retinal regions, and in stage 3, the ridge is vascularized, red. Stage 4a corresponds to peripheral retinal detachment. In stage 4b, the fovea is also detached, and in stage 5, there is total retinal detachment in an open or closed funnel [3, 4].

"Plus" disease includes retinal vessel dilation and tortuosity, retinal hemorrhages and pupil rigidity [3, 4].

Separately from the features of the "classic" ROP described above, aggressive posterior ROP (AP-ROP) has been described with the following aspects: very severe "plus" disease, posterior location (most commonly zone 1, but also posterior zone 2), ill-defined or no ridge, rapid progression to stage 5 ROP [3, 4].

Also, there are two important terms that have to be defined: threshold and pre-threshold ROP. Threshold ROP includes: stage 3, zone 1 or 2, with "plus" disease, with a ridge extending on more than five contiguous or eight cumulative clock hours. Pre-threshold ROP includes the following situations: less than threshold ROP in zone 1/stage 2, zone 2 with "plus"/stage 3, zone 2, without "plus"/stage 3 with "plus," less extended than threshold ROP [3, 4].

2.3. Laser effect

Understanding laser technology starts from the translation of the word LASER: light amplification by the stimulated emission of radiation.

Atoms occupy various energetic levels. Lower energetic levels are associated with higher stability. If the atom absorbs energy under the shape of a photon, it "jumps" on a higher energetic level in a state of excitation. The excited atom can "fall" back spontaneously on the lower energetic level by emitting a photon. The excited atom can be "forced" to fall from the higher on the lower energetic level if it meets a photon carrying the energy equal to the difference between the two levels. This process is called stimulated emission: a photon stimulates the emission of another photon [5].

If we would be able to bring the majority of atoms on the superior energetic level, the incident radiation will induce the emission of a more intense beam than the incident one. This is called radiation amplifying. The key problem is to obtain a state with more atoms on the superior energetic level, which is called population inversion and is reached by pumping. In order to amplify the light, the system is closed between two parallel mirrors forming a cavity. The mirrors allow photons to jump back and forth by continuously reflecting between them, thus producing stimulated emissions. When the radiation flux becomes extremely intense, it is allowed to get out of the cavity as laser beam [5].

The abovementioned principles explain the key properties of the laser radiation:

1. Because the photons are emitted through energies that are liberated between two well-defined energetic levels, the radiation is *monochromatic.*
2. Because the two mirrors are parallel, the laser beam is composed of highly parallel rays: *limited divergence.*
3. The emitted and the "disruptive" radiations are always in the same phase; therefore, the laser radiation is *coherent.*

These properties offer theoretical advantages to the laser radiation over the white light that are translated by its clinical applications in various ocular diseases [5].

Monochromatic laser light allows the specific selection of a wavelength that is going to be absorbed by a specific pigment in the eye according to the ocular condition.

Also there is no chromatic aberration allowing the obtainment of a small retinal impact.

Laser light is much more intense, which makes it possible to use low energies to obtain a clinical effect with a significantly lower risk for complications.

Parallelism allows the obtainment of small retinal lesions in the periphery.

Therapeutic energy can be pre-selected by the ophthalmologist according to the effect on the retina: lower energies are used initially which are progressively increased, up to the moment where the desired effect is obtained [5].

2.4. Laser retinal photocoagulation

Clinical effects of laser photocoagulation are obtained by thermal reaction. When the temperature in the tissue reaches a critical level, proteins are denatured and coagulation occurs. The factors that influence the results of coagulation for a certain power are: the energy of a specified wavelength, the spot size and the exposure time. According to the degree of coagulation, ocular reaction manifests by cell proliferation, cell migration, and scar formation [5].

Tissue effects of lasers depend upon the interaction between the laser wavelength and ocular pigments: melanin, hemoglobin and xanthophyll.

Melanin is found in the RPE as melanosomes and in the choroid as granules. The maximum absorption of melanin is for wavelengths of 400–600 nm, followed by blue, green, red and infrared. Subsequently, shorter wavelengths are better absorbed by melanin as compared to longer ones. When it comes to the penetration through tissues of the laser radiation, longer wavelengths will manifest their effect deep in the choroid. Because the quantity of melanin varies between individuals and from one region to another of the fundus, the coagulation effect of longer wavelengths is unequal. Longer wavelengths require higher energies to obtain similar effects with the shorter ones.

Hemoglobin is more selective in terms of absorption. Its maximum absorption is for blue, green and yellow wavelengths, whereas for red and infrared, there is no absorption.

Xanthophyll pigment is located exclusively in the fovea, and it absorbs the blue and blue-green laser radiations. Because of the damaging effects on the central vision of these radiations, they are no longer used in the clinical practice [5].

Lasers that create thermal reactions have direct and indirect effects on the ocular tissues.

In ischemic retinopathies, such as ROP, the indirect effect is used to induce the regression of new vessels that appear due to retinal ischemia.

Several mechanisms of action have been described. It is postulated that tissue destruction by laser photocoagulation decreases the need for oxygen of the tissues, and in the same time, it lowers the stimulus for the production of angiogenic factor.

http://dx.doi.org/10.5772/intechopen.79828

Photocoagulation also eliminates the photoreceptor cells, which are high oxygen consumers, allowing the use of available oxygen by the viable cells.

A tight adhesion between the retina and choriocapillaris is created following laser photocoagulation, increasing oxygen flow to the retina.

The pigmented cells destroyed by laser liberate a substance that inhibits angiogenesis [5].

2.5. Technical characteristics of the indirect diode laser

Diode laser has an infrared emission (810 nm), and it cools in the environment and has a life span of 30,000 h. The transmission optic system is very simple: it is constituted by mirrors leading the laser beam from the slit lamp to the patient's retina. When attached to the indirect ophthalmoscope, such as in the ROP treatment, this role is taken by a system of fiber optics.

The laser fiber is connected from the laser to the indirect ophthalmoscope, and the laser impacts are delivered by acting on a pedal, which is also connected to the laser. The console allows the operator to choose the adequate parameters of the laser impact: dimension, exposure time and power. The operator wears the helmet throughout the treatment and moves his head in order to deliver the light from the indirect ophthalmoscope and the laser beam into the infant's eye (**Figure 1**).

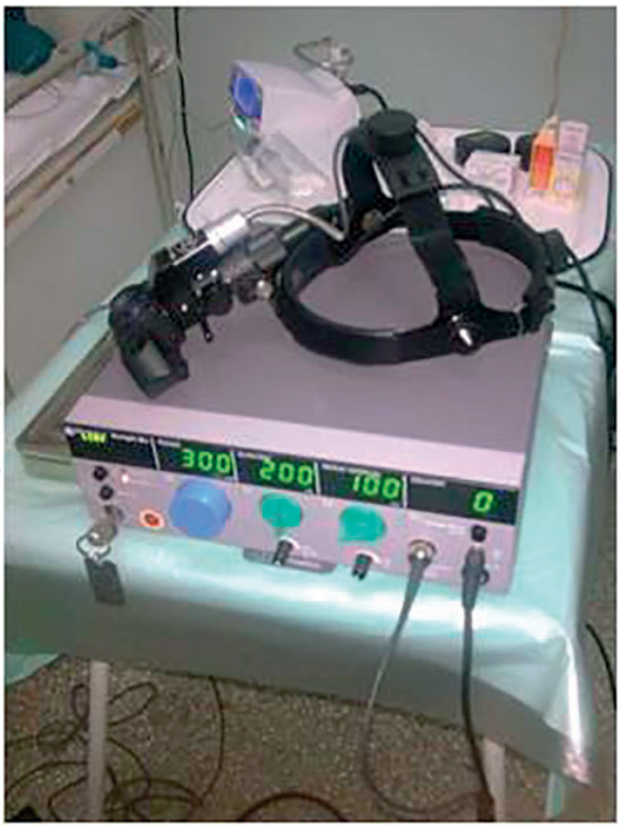

Figure 1. Indirect diode laser.

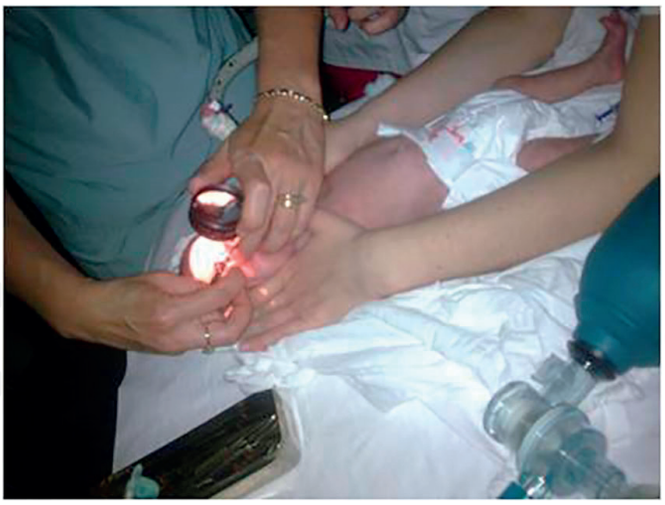

Figure 2. Delivery of the laser treatment.

The delivery mode is chosen: repeat at various intervals/single impact and the number of impacts is counted. The repeat mode is preferred because when pressing the pedal once, a series of impacts is delivered on the retina, at time intervals that are selected by the operator. However, this more rapid modality of treatment is chosen by the experienced surgeons. The retina is visualized with a +20 or +28 diopter lens and the peripheral retina is reached by the help of a scleral indentor (**Figure 2**).

2.6. Parameters used during the laser retinal photocoagulation

The clinical effect of laser photocoagulation on the retina depends on two main parameters: power and exposure time. If low power is used, higher exposure time is required. On the contrary, at high power, a low exposure time is sufficient to obtain a significant retinal reaction [5].

2.6.1. Power

Power is the parameter that influences the most the photocoagulation effect. Selecting a certain power is relative, as it depends on individual factors: retinal pigmentation, edema, pre-retinal fibrosis, the presence of vitreous hemorrhage. Therefore, the key element in choosing a certain laser power is clinical (retinal reaction), not technical (mW). Usually, treatment is initiated with low powers (150–200 mW) in order to test retinal reaction, never on pigmented retina. If there is no visible mark, power is increased with 20–50 mW, until the obtainment of the desired effect: whitish lesion. When high powers are used, the lesion appears gray with well-defined margins and sometimes in its center a vapor stream is emitted. This effect can be identified when passing from a thicker to a thinner retina, for example from the posterior pole toward the periphery, without reducing the power accordingly. During retinal photocoagulation, power must be varied in order to obtain the appropriate tissue reaction [5].

2.6.2. Exposure time

Exposure time can vary between 50 ms and 1 s. At low exposure times, the effect in the tissue is cylindrical: the area of the lesion is the same at the superficial (RPE) and deep (choroid) levels.

However, at low exposure times, high powers are required in order to obtain a clinical effect. This is associated with the risk of explosive effects. Usually, exposure times between 200 and 500 ms are preferred [5].

2.6.3. Dimension of the laser spot

When laser energy is delivered through the indirect ophthalmoscope, the dimension of the laser spot effectively arriving on the retina is the result of the distance between the helmet (the site where the laser fiber is fixed) and the retina [5].

2.6.4. Number of the laser spots

The number of laser spots is correlated with the area of nonvascular retina. Practically, all the surface of non-vascular retina should be destroyed by laser. By consequence, more the disease is posterior, more laser spots are needed. ROP represents an instance in which all photocoagulation must be completed in one session due to its rapid progression. The number of laser spots may vary between 1000 and 5000/eye [5].

2.6.5. Evolution of laser impacts

At the moment of application, the laser marks should be whitish. During the next days, they become less net because of the inflammatory reaction, which is proportional to the extension of treatment. Within 1–2 weeks, the impacts develop pigment in the central area surrounded by atrophy. The extension of scars at the fovea in posterior ROP may induce significant loss of vision [5].

2.7. Rationale for laser use in the treatment of ROP

The premature retina is incompletely developed and when exposed to high levels of oxygen which is necessary for life support, a relative hyperoxic environment is created, leading to the decrease of VEGF and subsequent delay or even cessation in the development of retinal vessels. By consequence, the retinal tissue does not get enough oxygen (relative hypoxia) and synthesizes angiogenic factor with the development of new vessels at the limit between the vascular and nonvascular retina.

The rationale of laser use in ROP is to destroy the nonvascular retina, which is the source of new vessels, thus interrupting the pathogenic chain ultimately leading to vision loss.

Cryotherapy was used before laser to destroy the nonvascular retina, and its results were first published in 1988 by the Cryo-ROP Study proving its efficacy in preventing ROP-related blindness [6].

A few years later, in 1994, the Laser Study Group demonstrated the laser was as effective as cryotherapy in preventing blindness produced by ROP and with less severe side effects. Besides the fact that it causes less trauma and manipulation on the globe as compared to cryotherapy, laser was more effective in zone 1 and zone 2 disease [2, 7].

2.8. Indications for laser treatment in ROP

The indications for ROP treatment were formulated for the first time by the Multicenter Trial of Cryotherapy for ROP, as a threshold disease [6].

The Early Treatment for ROP Randomized Trial Study affirmed that the criteria for treatment defined as "threshold" may no longer be the ideal indication for treatment. Therefore, the criteria for "pre-threshold" ROP were defined with the recommendation to initiate treatment also in these circumstances. The results of treatment in the pre-threshold ROP were significantly better than the threshold ones [2, 8, 9].

2.9. Timing of laser treatment for ROP

ROP is a model of acute retinal ischemia that is self-limiting, but if not addressed urgently, it may lead rapidly to retinal detachment and loss of vision. Because the window of opportunity during which laser treatment is likely to have a positive result is very short, timely recognition is crucial for a good outcome [7, 8]. Therefore, active screening should be carried out according to very precise criteria [3].

Basically, treatment should be performed at the point in the natural history of the disease when neovascularization can be reversed because once vitreo-retinal traction is initiated, the disease can no longer be controlled [2]. Therefore, knowing the correlation between the evolution of ROP and time is crucial for a correct screening.

The most vulnerable period, when ROP is at high risk of rapid progression starts at 34–35 weeks PCA up to 36–37 weeks PCA [8]. Usually, ROP does not develop during the first 2 weeks of life. The median age for the detection of stage 1 ROP is 34 weeks PCA, pre-threshold ROP appears around 36 weeks PCA and threshold ROP at about 37 weeks PCA. The vascularization of the retina is completed by 40–44 weeks PCA.

In conclusion, the interval for ROP detection is between 32 and 40 weeks PCA, but the critical phase, during which ROP may progress rapidly and has to be treated, is between 34 and 37 weeks PCA [7].

2.10. Indirect diode laser photocoagulation for ROP

Laser therapies are carried out in the Neonatology Units, under sedation. Prior laser treatment, pupil dilation is achieved with a mixture of tropicamide 0.5% and phenylephrine 2.5%. The eyes are maintained open with a lid speculum throughout the procedure, the retina is visualized with a +20 or +28 diopter lens and the peripheral retina is accessed with a scleral indentor.

Diode laser has an infrared emission of 810 nm, which is delivered transpupillary. Usually, the following laser parameters are used: 200 microns laser spot, with 200 ms duration and power between 100 and 300 mW, according to the retinal reaction. Laser spots are applied on all the surface of the non-vascular retina, from the anterior margin of the ridge to the ora serrata, in a confluent manner, with no space between them.

Adverse events related to laser treatment were cited in the literature: anterior uveitis, cataract, vitreous hemorrhage, retinal detachment [7]. Anterior uveitis was rarely identified in cases that required extensive laser photocoagulation, such as aggressive posterior-ROP [2]. The risk of cataract development is very low, especially when using the infrared laser which is absorbed deep into the choroid and not in the crystalline lens [2, 7]. Vitreous hemorrhage and retinal detachment represent rather a failure of laser to stop ROP progression than a complication by itself [2].

2.11. Advantages of indirect laser photocoagulation over cryotherapy for ROP treatment

Cryotherapy was the first method that stopped the progression of ROP toward blindness [6]. The rationale was to destroy the non-vascular retina by applications of cryo on the sclera.

Indirect laser photocoagulation of the retina proved to be as effective as cryo in preventing ROP-related blindness, but with significantly fewer side effects. The pressure exerted by the cryoprobe on the infants' sclera was associated with high risk of myopia. Cryotherapy itself is more laborious than laser and requires more time and general anesthesia. By consequence, more anesthesia-related incidents were reported during cryo as compared to laser. In posterior ROP, it is very difficult (sometimes impossible) to reach the retina in the posterior pole with the cryoprobe. Therefore, posterior non-vascular retina may remain untreated with a high risk of ROP progression.

For all these reasons, currently indirect laser photocoagulation replaced cryotherapy in the treatment of ROP in most of settings.

ROP offers an eloquent example in which laser energy has revolutionized the treatment of an extremely serious disease, with significant socioeconomic and life quality positive impact.

3. Personal experience in the treatment of ROP with indirect diode laser

3.1. Setting

This study was carried out at the "Iuliu Hatieganu" University of Medicine and Pharmacy (Cluj-Napoca, Romania) in the Ophthalmology and Neonatology Departments. All laser therapies were performed by two ophthalmologists in the Neonatology Department. Before enrollment in the study, informed consent was obtained from the parents/tutors. The study is approved by the Ethical Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy.

3.2. Study sample

This study includes all the consecutive premature infants with ROP who required laser photocoagulation between January 1, 2006 and December 31, 2017. The screening protocol was based on the following criteria: GA less or equal to 33 weeks and, BW less or equal to 1500 g.

Premature infants beyond these criteria were also included in the screening if other risk factors were associated: prolonged oxygen administration with saturation over 93%, repeated transfusions, sepsis and the need of more than 6 days of mechanical ventilation for cardio-respiratory support. Eyes with stage 2 zone 2, stage 4a, 4b and 5 were not treated by laser and were therefore not included in the study sample.

3.3. Medical intervention

We performed laser therapy in the following situations: stage 3 zone 1 ROP, stage 3 zone 2 ROP, stage 2 zone 1 ROP and AP-ROP. Infants with AP-ROP were treated within 24 h from diagnosis and the rest of them within 48 h from diagnosis.

All laser therapies were carried out under sedation in the Neonatology Unit. We used a portable indirect diode laser, with an emission of 810 nm, and laser energy was delivered transpupillary (**Figure 1**).

A mixture of tropicamide 0.5% and phenylephrine 2.5% was instilled preoperatively, in order to dilate the pupils. In order to gain access to the retina, a lid speculum, a sclera indentor and a + 28 diopter lens were used (**Figure 2**).

Indirect diode laser photocoagulation was performed with the following parameters: 200 microns laser spot, 200 ms duration and 150–300 mW power, according to the retinal reaction. The obtaining of a whitish retinal spot was aimed. Laser spots were applied in a confluent manner, with no space between impacts, to cover all the surface of the non-vascular retina, up to ora serrata. The number of impacts varied between 1500 and 4000/eye.

The first postlaser review took place 7 days after treatment. In case of regression, examinations continued every 5–6 days, until there was clear evidence of ROP regression. In case of regression failure, laser was completed immediately. The treated eyes were monitored with a frequency dictated by the clinical course of the disease, in order to address any risk of sequel.

3.4. Statistical analysis

Epi Info 7 software (Centers for Disease Control and Prevention, Atlanta, GA) was used for the statistical analysis of the data. Frequencies for the following independent variables concerning the premature infant were calculated: gender, GA, BW, type of pregnancy (unique or multiple), PCA and PNA at treatment, ROP classification.

Odds ratio was used to interpret the results, and statistical significance was evaluated according to P value calculated with t test. Chi-square test was used if values over 5 were expected in 80% of the table cells, and Fisher exact test was used if values under 5 were expected in more than 20% of the table cells. P values less than .05 were considered statistically significant.

3.5. Results

In the previously mentioned period, we treated by indirect diode laser photocoagulation 110 premature infants of which, 60 were males (54.54%) and 50 were females (45.45%).

Of these, 35 were from Cluj (31.81%) and 75 came from neighboring departments where laser was unavailable (68.18%).

GA was between 24 and 33 weeks (mean ± standard deviation: 28.30 ± 2.87 weeks) and BW was between 500 and 1700 g (mean ± standard deviation: 1121 ± 280.45 g).

Of the 110 preterm infants, 74 were the result of single pregnancies (67.27%) and 36 of multiple pregnancies (32.72%).

PNA at treatment was between 5 and 13 weeks (mean: 8.38 ± 1.93 weeks) and PCA at treatment was between 32 and 41 weeks (mean: 37.02 ± 1.65 weeks).

The data are summarized in **Table 1**.

Retinal laser photocoagulation was bilateral in 100 cases and unilateral in 10 cases, which makes for 210 lasered eyes. The 10 eyes in which laser photocoagulation was not performed fall into one of the following categories: stage 1 zone 2 ROP (four eyes), stage 2 zone 2 ROP (three eyes), stage 4a ROP (one eye), stage 5 ROP (one eye) and congenital atrophy (one eye). The three eyes with stage 2 zone 2 ROP were followed up closely, every 3 days and they regressed spontaneously with no need for laser therapy. ROP classification of the lasered eyes is as follows: stage 3 zone 2 ROP—167 eyes (79.52%), stage 3 zone 1 ROP—30 eyes (14.28%), AP-ROP—13 eyes (6.19%).

ROP regressed after laser treatment in 185 eyes (88.09%). Of the 185 eyes, regression was achieved after one laser session in 175 eyes (94.59%) and after two laser sessions in 10 eyes (5.40%). In all ROP cases with stage 3 zone 2 disease, regression was obtained after one laser

Characteristic	No
Gender	
Male	60 (54.54%)
Female	50 (45.45%)
City of origin	
Cluj	35 (31.81%)
Outside Cluj	75 (68.18%)
Type of pregnancy	
Single	74 (67.27%)
Multiple	36 (32.72%)
Mean ± SD gestational age (wk)	28.30 ± 2.87
Mean ± birth weight (g)	1121 ± 280.45
Mean ± SD PNA at treatment (wk)	8.38 ± 1.93
Mean ± SD PCA at treatment (wk)	37.02 ± 1

SD, standard deviation; PNA, postnatal age; PCA, postconceptional age.

Table 1. Premature infants treated by indirect diode laser photocoagulation for ROP.

session. In stage 3 zone 1 ROP cases, regression was achieved after one laser session in 26 eyes, whereas in four eyes, two laser sessions were required to stabilize the disease. In AP-ROP cases, two laser sessions were necessary in 6 of the 13 eyes. Statistical tests proved that regression rate was significantly worse in AP-ROP eyes as compared with stage 3 zone 2 and stage 3 zone 1 ROP (odds ratio = 13.53, relative risk = 7.79, $P < .001$).

Within the group of 25 eyes in which ROP failed to regress, 14 belonged to the male gender (56%) and 11 to the female gender (44%). The difference is not statistically significant.

The type of pregnancy (single or multiple) did not influence the outcome: ROP regressed in 132 of the 149 treated eyes coming from single pregnancies (88.59%) and in 53 of the 61 eyes coming from multiple pregnancies (86.88%).

Macular dragging was identified in three eyes, all from the AP-ROP group. Complications related to laser treatment were represented by two cases of mild anterior uveitis that responded promptly to mydriatic and anti-inflammatory eye drops.

We evaluated the timing of the laser treatment according to two parameters: PNA and PCA at treatment. Treatment was performed at PNA of 8 weeks or less in 118 eyes (56.19%) and at PNA of more than 8 weeks in 92 eyes (43.80%). Within the first group, ROP regressed in 101 eyes (85.59%), and within the second group, ROP regressed in 84 eyes (91.30%). According to the chi-square test, the difference is not statistically significant. PCA at treatment was equal or less than 37 weeks in 123 eyes (58.57%) and more than 37 weeks in 87 eyes (41.42%). Within the first group, ROP regressed in 112 eyes (91.05%), and within the second group, ROP regressed in 78 eyes (89.65%). This difference is not statistically significant, according to the chi-square test.

Within the group of 210 treated eyes, 84 belonged to premature infants with BW equal to or less than 1000 g (40%) and 126 eyes (60%), to premature infants with BW of more than 1000 g. ROP failed to regress in nine eyes from the first group (10.71%) and in 16 eyes from the second group (12.69%). The statistical tests proved that the difference is not significant.

GA was 28 weeks or less in 116 eyes (55.23%) and more than 28 weeks in 94 eyes (44.76%). Within the first group, ROP regressed after laser treatment in 104 eyes (89.65%) and in the second group ROP regressed in 81 eyes (86.17%). The difference is not statistically significant.

3.6. Discussion

The premature infants in our series who needed laser for the treatment of ROP had higher BW (1121 g) and older gestational ages (28 weeks) than their counterparts in the United States (830 g BW average and 26 weeks GA average). The oldest treated infant was born at 33 weeks PCA and the heaviest treated infant was 1700 g, both beyond the screening criteria in the United States. The practical impact of this observation is that each country/region has to apply its own screening criteria for ROP. If criteria from the USA or from Western Europe had been applied, many ROP cases had been lost with subsequent visual loss.

Because of the short window of opportunity during which the laser is effective, timely recognition of the disease is crucial for the positive result of the treatment. In our series, PCA and

PNA at treatment were not statistically significantly different between the favorable outcome and unfavorable outcome groups.

Indirect diode laser photocoagulation proved its efficacy in ROP treatment. Our ROP regression rate is comparable to the ones cited in the literature [7]. The laser spots were applied on all the surface of the nonvascular retina, from the anterior margin of the ridge (when identifiable) up to ora serrata. In six eyes, we also placed laser posterior to the ridge for two reasons: to limit the extension of traction toward the posterior pole and to destroy an area, which is known to provide high levels of vasoproliferative factors because it is ischemic. We used this approach only in situations with advanced stage 3 disease in which we identified traction on the retina. All the six eyes had a good outcome (ROP regressed with no anatomical sequelae). Not all authors approve this strategy, arguing that it destroys more of the peripheral visual field with no proven benefit [2].

We delivered laser energy transpupillary in all cases. Laser can also be delivered through the sclera. In terms of efficacy, the two delivery methods are similar, but the transscleral approach is more traumatic. According to some authors, the transscleral approach carries no risk of cataract formation. However, in our series, we identified no case of cataract after laser delivered transpupillary. This is logic, taking into account that the absorption site of the infrared radiation is deep into the choroid, passing through the crystalline lens without being absorbed.

Literature shows that lower GA and BW are associated with poorer outcomes of ROP [6]. These observations could not be verified in our series in which statistical tests proved no significant difference in terms of outcome according to GA and BW.

Our study proves that the only factor with significant impact on ROP prognosis following laser was the ROP type. As such, AP-ROP cases had a significantly worse outcome as compared to the so-called classic ROP ones, which is in agreement with results cited in the literature [10]. The disappointing results that we obtained in AP-ROP cases with laser photocoagulation motivated us to start treatment in these cases with intravitreal Bevacizumab. This attitude significantly improved our results.

4. Conclusion

Indirect diode laser photocoagulation of the non-vascular retina is a major tool in preventing ROP-related blindness. In order for the laser treatment to be effective, proper screening and timely recognition of ROP are crucial. Intravitreal anti-VEGF injections improved the outcome of laser treatment in severe forms of the disease, but laser remains the golden standard in the treatment of ROP.

Acknowledgements

This study was funded by grant number PED 156, Executive Agency for Higher Education, Research, Development and Innovation Funding, Romania.

Conflict of interest

The author declares no conflict of interest related to the publication of this chapter.

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