Regression Rates Following the Treatment of Aggressive Posterior Retinopathy of Prematurity with Bevacizumab Versus Laser: 8-Year Retrospective Analysis

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Background: Retinopathy is a serious complication related to prematurity and a leading cause of childhood blindness. The aggressive posterior form of retinopathy of prematurity (APROP) has a worse anatomical and functional outcome following laser therapy, as compared with the classic form of the disease. The main outcome measures are the APROP regression rate, structural outcomes, and complications associated with intravitreal bevacizumab (IVB) versus laser photocoagulation in APROP.

Material/Methods: This is a retrospective case series that includes infants with APROP who received either IVB or laser photocoagulation and had a follow-up of at least 60 weeks (for the laser photocoagulation group) and 80 weeks (for the IVB group). In the first group, laser photocoagulation of the retina was carried out and in the second group, 1 bevacizumab injection was administered intravitreally. The following parameters were analyzed in each group: sex, gestational age, birth weight, postnatal age and postmenstrual age at treatment, APROP regression, sequelae, and complications. Statistical analysis was performed using Microsoft Excel and IBM SPSS (version 23.0).

Results: The laser photocoagulation group consisted of 6 premature infants (12 eyes) and the IVB group consisted of 17 premature infants (34 eyes). Within the laser photocoagulation group, the evolution was favorable in 9 eyes (75%) and unfavorable in 3 eyes (25%). Within the IVB group, APROP regressed in 29 eyes (85.29%) and failed to regress in 5 eyes (14.71%). These differences are statistically significant, as proved by the McNemar test ($P<0.001$).

Conclusions: The IVB group had a statistically significant better outcome compared with the laser photocoagulation group, in APROP in our series.

MeSH Keywords: Intravitreal Injections • Laser Therapy • Retinopathy of Prematurity

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Background

Retinopathy is a serious complication related to prematurity and a leading cause of childhood blindness [1]. The rate of blindness associated with retinopathy of prematurity (ROP) varies according to the country: 3% in the United Kingdom, 13% in United States, and higher in the middle income countries and in the rapidly developing economies of India and China [2].

In most cases, ROP regresses spontaneously, but severe disease leads to retinal detachment and sight loss, if not treated promptly. Laser photocoagulation of the non-vascularized retina is the standard cure for ROP, with a regression rate of over 90% [3,4]. However, in the aggressive posterior retinopathy of prematurity (APROP), the group for early treatment of ROP (ET-ROP) reported 15% unfavorable functional outcome and 10% unfavorable structural outcome with laser, due to the development of retinal folds, retinal detachment, and retrolental fibroplasia [5]. Over the last years, the intravitreal injection of anti-vascular epithelial growth factor (VEGF) has become increasingly popular in ROP. Mintz-Hittner published the first prospective, controlled, randomized trial that proved a significantly lower recurrence rate of ROP following intravitreal bevacizumab (IVB), compared with laser photocoagulation, especially in zone I ROP [6]. Although this study brought a new approach of ROP treatment, it received several criticisms and neither long-term local effects, nor safety of IVB are well known. In a previous publication, we reported an 85.13% regression rate following bevacizumab intravitreal monotherapy in zone I stage 3+ and APROP [7].

In the Ophthalmology Department of the Iuliu Hatieganu University of Medicine and Pharmacy from Cluj-Napoca, Romania, laser became available for ROP in 2006, and in 2009 we started to treat ROP with intravitreal injection of bevacizumab (Avastin, Genentech Inc, San Francisco, California, USA). The purpose of this study is to determine the relative effectiveness and major complications associated with IVB versus laser photocoagulation to treat APROP.

Material and Methods

This is a retrospective case series that includes all the consecutive infants with APROP who received either laser photocoagulation or IVB between January 1, 2006, and December 31, 2013, and had a follow-up of at least 60 weeks (for the laser group) or 80 weeks (for the IVB group). Overall, the follow-up ranged from 60 weeks to 144 weeks from the procedure, in our series.

Main outcome measures. APROP regression and the structural outcome associated either with laser photocoagulation or with IVB.

Setting

This study was undertaken in accordance with the declaration of Helsinki (1964). All the laser therapies were carried out by 2 ophthalmologists, in the Neonatology Department belonging to the Iuliu Hatieganu University of Medicine and Pharmacy from Cluj-Napoca. All the intravitreal injections were performed by the same ophthalmologist, in the Departments of Neonatology and Ophthalmology belonging to the Iuliu Hatieganu University of Medicine and Pharmacy from Cluj-Napoca and in the Departments of Neonatology belonging to the Saint Pantelimon and Polizu Hospitals from Bucharest, Romania. Both types of treatment (laser photocoagulation or IVB) were conducted only after having obtained the informed consent from the parents/tutors. The study was approved by the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy.

Study sample

The data of the infants treated either with laser photocoagulation or with IVB for APROP between January 1, 2006, and December 31, 2013, were recorded. Before 2009, for the treatment of ROP we used only laser. Starting in 2009, our first-line treatment for APROP became IVB. We compare retrospectively 2 groups of patients diagnosed with APROP. In the first group, we included the infants with APROP treated between 2006 and 2009 by laser photocoagulation. In the second group, we included the consecutive infants with APROP treated between 2009 and 2013, by IVB.

We excluded from the study sample the patients coming from a specific neonatal intensive care unit (NICU) because they had a particularly bad outcome following laser, which made us suppose that the neonatal treatment protocol was different from that of other units. Moreover, babies from this NICU did not undergo intravitreal anti-VEGF in our department, because by the time we started IVB, ophthalmological treatment had become available in their unit.

Screening protocol for ROP

In Romania, we use the following screening criteria to detect ROP: gestational age (GA) less/equal to 33 weeks, birth weight (BW) ≤1500 g. Premature infants outside 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 necessity of more than 6 days of mechanical ventilation for the cardiorespiratory support.

Definition of APROP

APROP is categorized separately from classical ROP, with the following distinguishing features: very severe "plus disease," posterior location (most commonly in zone I but also possible in posterior zone II), ill-defined or no ridge, arteriovenous shunting throughout the posterior pole, dilated and tortuous vessels in a syncytial pattern [8].

Medical intervention

All the treatments (laser photocoagulation or IVB) were performed within 24 hours of the diagnosis. Before the intervention, the pupils were dilated with a mixture of tropicamide 0.5% and phenylephrine 2.5%. All the laser therapies were carried out in the neonatology department, under general anesthesia, with a portable diode laser photocoagulator, having the emission of 810 nm; the laser energy was delivered trans-pupillary in all cases. In order to get access to the retina, we used a lid speculum, a scleral depressor, and a +28-diopters lens. The parameters of the laser photocoagulation were 200 microns laser spots with 200 ms duration and 150 to 300 mW power. The total number of burns per eye varied from 3000 to 6000, in 1 or 2 sessions, with a mean of 4235. We did not exceed 4000 burns per eye in 1 session. The posttreatment review took place at 6 to 7 days from the treatment, and it continued every 5 to 6 days, until there was evidence of ROP regression. Retreatment was performed 7 to 10 days after the initial treatment, if ROP failed to regress. The treated eyes were monitored at a frequency dictated by the clinical condition to determine the risk of sequelae.

The intravitreal injections of bevacizumab were performed according to the following protocol: for anesthesia, 0.5% propara-caine hydrochloride was administered topically, 3 times, every 2 minutes before the injection. In each eye, 5% povidone iodine was instilled 3 minutes before the injection. A nurse held the infant's head during the procedure and 0.025 mL of bevacizumab (0.625 mg) were injected in each eye, in 1 session, in pars plicata, 1.5 to 1.75 mm away from the limbus, with a 30 G needle, perpendicularly on the globe initially and then slightly directed toward the center of the eyeball. After the injection, topical tobramycin was administered, 5 times/day for 3 days. The patients were reexamined the next day and then every week to monitor the regression of the disease.

Follow-up

Within the laser photocoagulation group, the follow-up continued every month, for at least 60 weeks after treatment. Within the IVB group, the follow-up continued for at least 80 weeks, every 2 weeks, during the first 3 months, and then every month. Full vascularization of the retina was defined as

vascularization as far as it would develop without an active component or clinically significant tractional elements. The examinations were performed by 3 ophthalmologists experienced in ROP. All the patients were followed for long-term systemic complications.

Anatomical outcome

In order to evaluate the anatomical outcome, we used indirect ophthalmoscopy. We considered as positive signs, the pupil dilation, the disappearance or decrease of retinal vessel tortuosity, and neovascularization. Within the IVB group, the growth of the normal retinal vessels toward the peripheral retina was observed. Worsening of ROP was defined as the persistence or reappearance of plus disease and of retinal neovascularization and the progression toward retinal detachment. In all of these situations, conventional laser photocoagulation of the retina was carried out, when possible. Pictures of the retina before and after treatment were taken with a Ret Cam (Clarity Medical System, Pleasanton, California, USA).

Statistical analysis

Statistical analysis was performed using Microsoft Excel and IBM SPSS (version 23.0). Data were presented as mean, median, standard deviation (SD) for the groups. Shapiro-Wilk test for normality, Levene test for equality of variances, *t* test, McNemar test, and the Mann-Whitney U test were used for statistical analysis. $P<0.05$ was regarded as significant.

In order to compare the intrapatient variance with the interpatient variance in both laser photocoagulation and IVB treatment groups, we calculated the coefficient of variation for GA, BW, postnatal age (PNA), and postmenstrual age (PMA) and the distribution between groups regarding the sex and the type of pregnancy.

Results

The laser photocoagulation group included 6 APROP infants (12 eyes) and the IVB group, 17 APROP infants (34 eyes).

Descriptive statistics of the 2 groups

Table 1 summarizes the data of the 2 treated groups. All quantitative variables were normally distributed; Shapiro-Wilk test probability was above 0.05. Tables 2 and 3 present the data of all the infants with APROP who were treated by laser photocoagulation and IVB, respectively.

In both groups (laser and IVB), the treatment was bilateral.

Table 1. Data of the APROP treated infants.

	Laser group		IVB* group		Statistical tests	
					Chi-square	Fisher exact
Gender						
Males	5	(83.33%)	7	(41.18%)	p=0.076	p=0.156
Females	1	(16.66%)	10	(58.82%)		
Type of pregnancy						
Single	6	(100%)	16	(94.12%)	p=0.544	p=1.000
Multiple	0		1	(5.88%)		
					Levene test	**T test equal variances assumed**
GA (weeks, mean ±SD**) (median, range)	29.83±1.83 31 (27–31)		28.29±1.53 28 (26–32)		p=0.340	p=0.057
GA coefficient of variation	6.15%		5.41%			
BW (grams, mean ±SD) (median, range)	1198.33±235.58 1165 (950–1500)		1094.71±216.39 1010 (900–1800)		p=0.546	p=0.335
BW coefficient of variation	19.66%		19.77%			
PNA at treatment (weeks, mean ±SD) (median, range)	6.50±0.55 6.50 (6–7)		6.12±1.11 6 (4–8)		p=0.213	p=0.433
PNA coefficient of variation	8.43%		18.17%			
PMA at treatment (weeks, mean ±SD) (median, range)	36.33±1.51 37 (34–38)		34.41±1.58 34 (31–37)		p=0.928	p=0.017
PMA coefficient of variation	4.14%		4.60%			

* Intravitreal bevacizumab; ** Standard deviation.

Group comparability

Our first goal was to find out whether there are significant differences between the 2 groups treated by 2 different methods, regarding the above-mentioned parameters, and that the intragroup variations are minimal. Because the coefficient of variation for GA, BW, PNA, and PMA was under 20% (Table 1), those variables are homogenous or relatively homogenous. No significant differences in distribution between groups was observed regarding the sex or the type of pregnancy.

No significant differences were observed between IVB and laser photocoagulation groups, for the mean values of GA, BW, or PNA. The only valid difference between the 2 groups was the mean of PMA (36.33 weeks for laser photocoagulation, versus 34.41 weeks for IVB; Table 1).

Evolution after treatment within the 2 groups

The laser photocoagulation group included 12 eyes and the IVB group, 34 eyes.

Within the laser photocoagulation group, the evolution was favorable in 9 eyes (75%) and unfavorable in the remaining 3 eyes (25%). Within the IVB group, APROP regressed in 29 eyes (85.29%) and failed to regress in 5 eyes (14.71%). Those observed differences are statistically significant, as proved by McNemar test, $P<0.001$. Laser photocoagulation had to be repeated in 1 of the 6 cases with APROP (2 eyes, 16.66%). The 2 eyes were saved with retreatment. The laser spots were applied on the skipped areas located toward the macular region.

The pictures belong to an APROP case treated by laser photocoagulation, referred from the NICU that was excluded from the present study. The infant had a GA of 26 weeks and BW of 760 g. Laser photocoagulation was carried out 9 weeks after birth, at PMA of 35 weeks.

In Figures 1 and 2, prelaser aspects are presented. In both eyes, the retinal vessels are short, moderately dilated, and very tortuous; no ridge is visible; and arteriovenous shunts are identified throughout the posterior pole. Temporal vessels are more dilated than the nasal ones. Retinal hemorrhage is

Table 2. Data of each APROP infant treated by laser photocoagulation.

Case	Gender	GA (weeks)	BW (g)	PNA (weeks)	PMA (weeks)	Outcome (OD/OS)
1	M	31	1500	6	37	Good/good
2	M	31	1130	6	37	Bad/bad
3	M	31	1450	7	38	Good/good
4	F	28	950	7	35	Good/good
5	M	27	960	7	34	Good/good
6	M	31	1200	6	37	Bad/good

Table 3. Data of each APROP infant treated by IVB.

Case	Gender	GA (weeks)	BW (g)	PNA (weeks)	PMA (weeks)	Outcome (OD/OS)
1	M	28	900	8	36	Good/bad
2	F	28	1000	5	33	Good/good
3	F	32	1800	4	36	Good/good
4	F	26	1100	5	31	Good/good
5	F	28	990	6	34	Good/good
6	F	29	1140	8	37	Good/bad
7	F	27	970	6	33	Good/good
8	F	29	1070	6	35	Good/good
9	F	28	990	7	35	Good/good
10	M	28	1000	6	34	Good/good
11	F	30	1030	6	36	Good/good
12	M	31	1240	5	36	Good/good
13	M	27	1010	7	34	Good/good
14	F	27	950	7	34	Bad/bad
15	M	27	980	5	32	Good/good
16	M	28	1390	7	35	Good/bad
17	M	28	1050	6	34	Good/good

also identified inferiorly, in each eye. The macular region is not completely developed. The black and white images depict better the contrast between the vascularized and nonvascularized retina and identify the extent of avascular retina.

Figures 3 and 4 were taken 10 days after laser photocoagulation. In both eyes, the retinal vessels were less tortuous than before laser, but they were still dilated, mainly the temporal ones. The laser scars were pigmented and skipped areas were visible,

especially toward the macular region. A second laser session was proposed, but the parents refused and went abroad. Retreatment was not performed in due time, and the case had a poor outcome.

Within the IVB group, APROP regressed in 29 eyes (85.29%) and failed to regress in 5 eyes (14.71%). Laser photocoagulation of the retina could be performed in 3 of these 5 eyes, with favorable outcome in all of them. In the remaining 2 eyes, the poor visualization made laser treatment impossible.
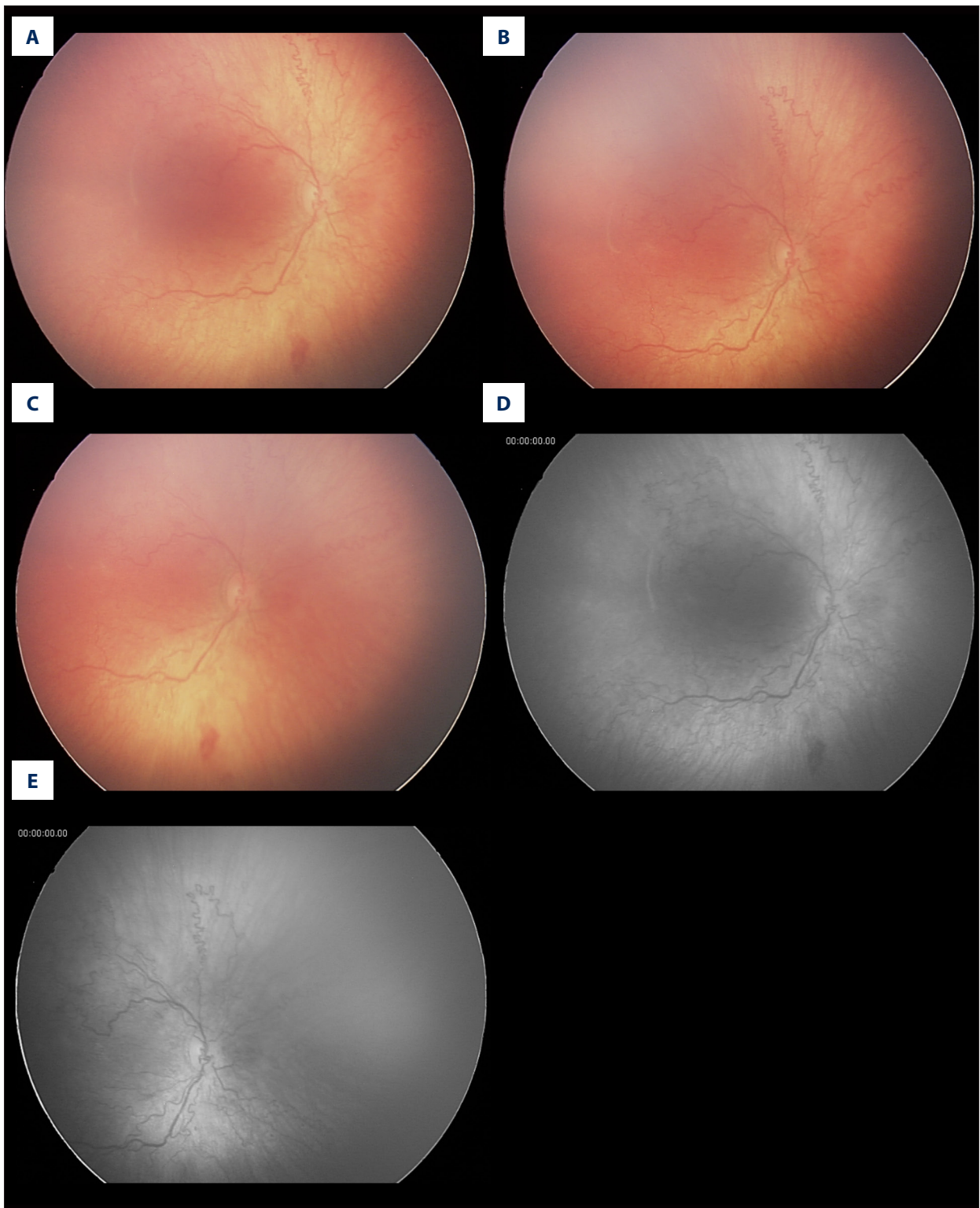
Figure 1. (A) RE – very tortuous, moderately dilated retinal vessels in the posterior pole, no visible ridge, the temporal retinal vessels are more dilated than the nasal ones; **(B)** RE – arterio-venous shunting throughout the posterior-pole; **(C)** RE – inferior retinal hemorrhage; **(D, E)** RE – the black and white images identify more clearly, the limit between the vascularized and non-vascularized retina, revealing the extent of avascular retina.
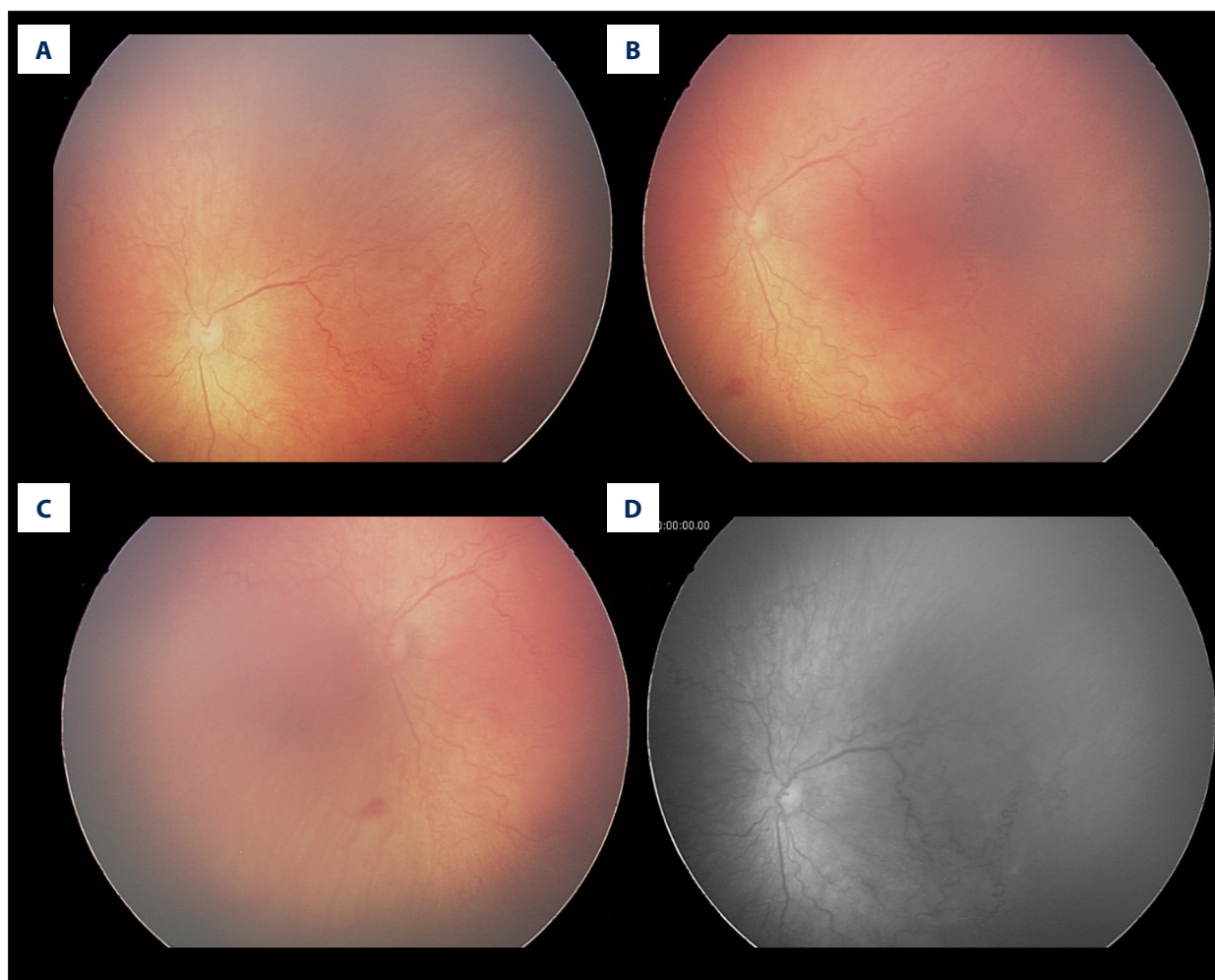
Figure 2. (**A**) LE – very tortuous, moderately dilated retinal vessels in the posterior pole, no visible ridge, the temporal retinal vessels are more dilated than the nasal ones; (**B, C**) LE – arterio-venous shunting and inferior retinal hemorrhage are visible; (**D**) LE – the black and white image displays better the arterio-venous shunts and reveal more clearly, the limit between the vascular and avascular retina.

From the IVB group, we selected 2 cases: 1 with good outcome bilaterally (case 12, Table 3) and 1 with good outcome unilaterally (case 6, Table 3).

Figures 5 and 6 belong to case 12 within the IVB group (Table 3). The infant was born at 31 weeks, with a BW of 1240 g and was treated with IVB bilaterally, 5 weeks after birth, at PMA of 36 weeks. APROP appears symmetric; the retinal vessels are very tortuous and short and form a syncytial pattern. There is no ridge, but arteriovenous shunting and an extensive area of avascular retina are visible. On the fifth day after IVB, there are obvious signs APROP regression: the retinal vessels are less tortuous, with normal caliber, and arteriovenous shunting is less obvious. The case was followed up to 100 weeks and had a good bilateral anatomical outcome.

Figures 7 and 8 belong to case 6 within the IVB group (Table 3). GA was 29 weeks, BW 1140 g; IVB injection was performed bilaterally, 8 weeks after birth, at PMA of 37 weeks. The presentation is asymmetric, the disease being more severe in the right eye (Figure 7A, 7B). Following IVB, APROP regressed in the left eye. Because of the poor visualization in the right eye, laser treatment could not be performed and disease progressed to stage 5 ROP. In Figure 8E, 8F, the retina in the left eye, 8 weeks following IVB, shows good anatomical outcome.

Comparative evolution after treatment between the 2 groups

The differences between the 2 groups are statistically significant, as proved by McNemar test (*P*<0.001; Table 4). The distribution per patient of APROP success rate of the IVB and laser photocoagulation treatment is presented in the same table.
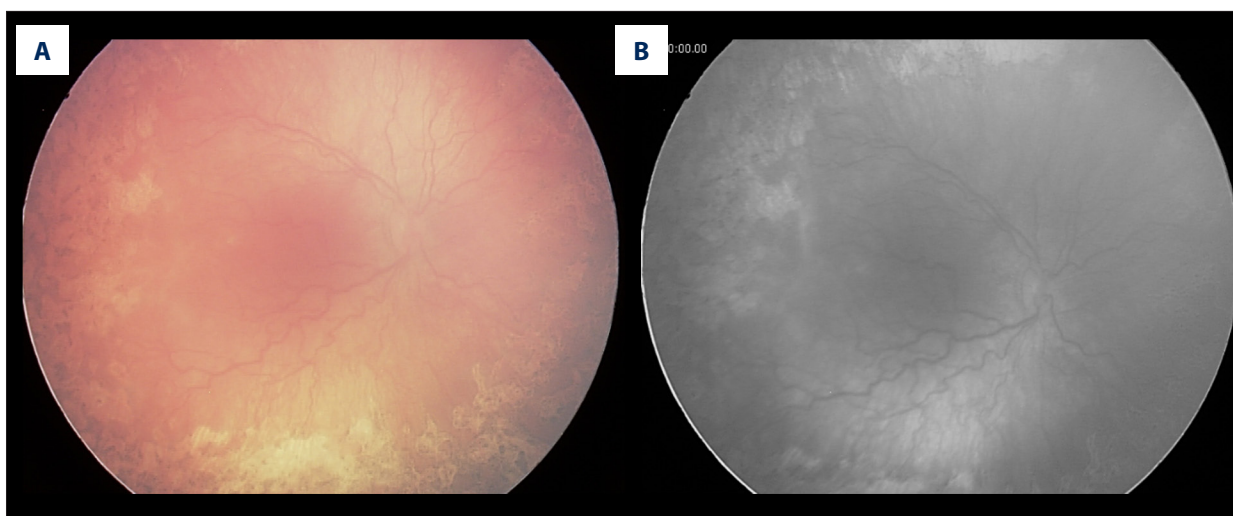
Figure 3. (**A, B**) RE (color and black and white image) – pigmented laser scars, persistence of dilated retinal vessels, especially in the temporal side, skipped areas towards the macular region.
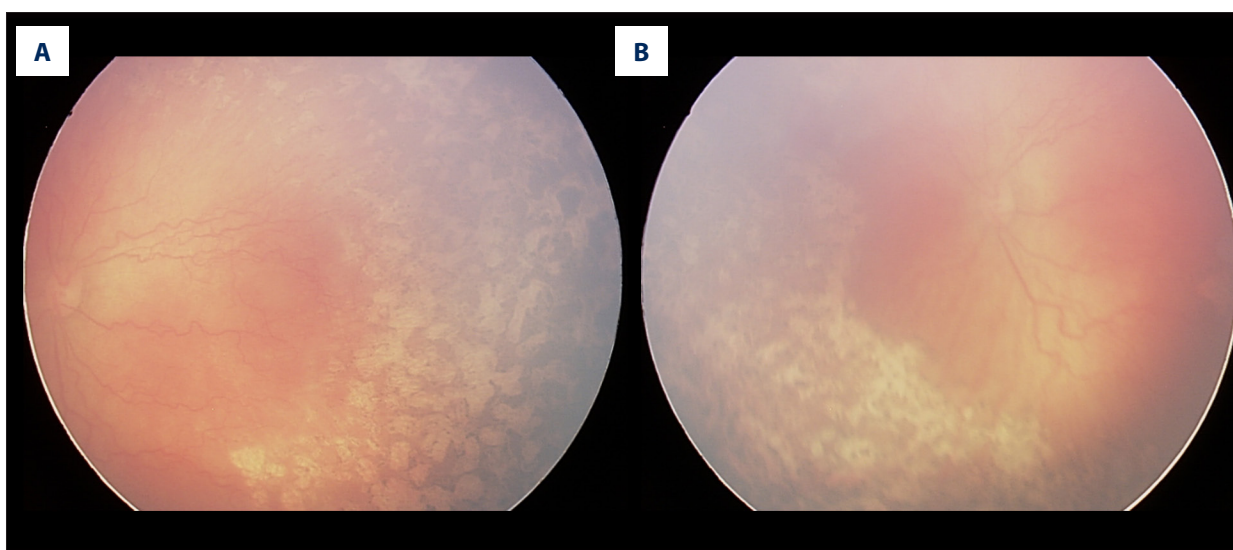

Figure 4. (**A**) LE – posterior pole and temporal retina - pigmented laser scars, skipped areas towards the posterior pole and macular region, retinal vessels still tortuous and moderately dilated; (**B**) LE – at the level of the nasal retina, no skipped areas are visible, the nasal vessels are less dilated than the temporal ones.

Global success rate (bilateral or unilateral regression) versus unsuccessful treatment was higher for IVB (94.12% of cases) against laser photocoagulation (83.33% of cases) and statistically significant (McNemar test, $P<0.001$).

We also observed that treatment worked in less time in the IVB group than in the laser photocoagulation group.

Characteristics of infants who did not respond to treatment

In order to find out if there were any characteristics of the infants who did not respond to treatment, we evaluated comparatively, within the 2 groups, the GA and BW in infants with good outcome, versus the ones with bad outcome. Because of the reduced size of samples, data reported by the Shapiro-Wilk test were not showing a normal distribution, so the analysis was performed with Mann-Whitney U test. The differences were not statistically significant, as shown in Table 5. We also compared the PNA and PMA at treatment between the infants with good outcome and the ones with bad outcome, within the 2 groups. No statistically significant differences were observed (Table 5).

The bad outcome was identified 1 week after treatment, in all 8 eyes within this series (3 from the laser photocoagulation group and 5 from the IVB group). We had no late recurrence in this series.
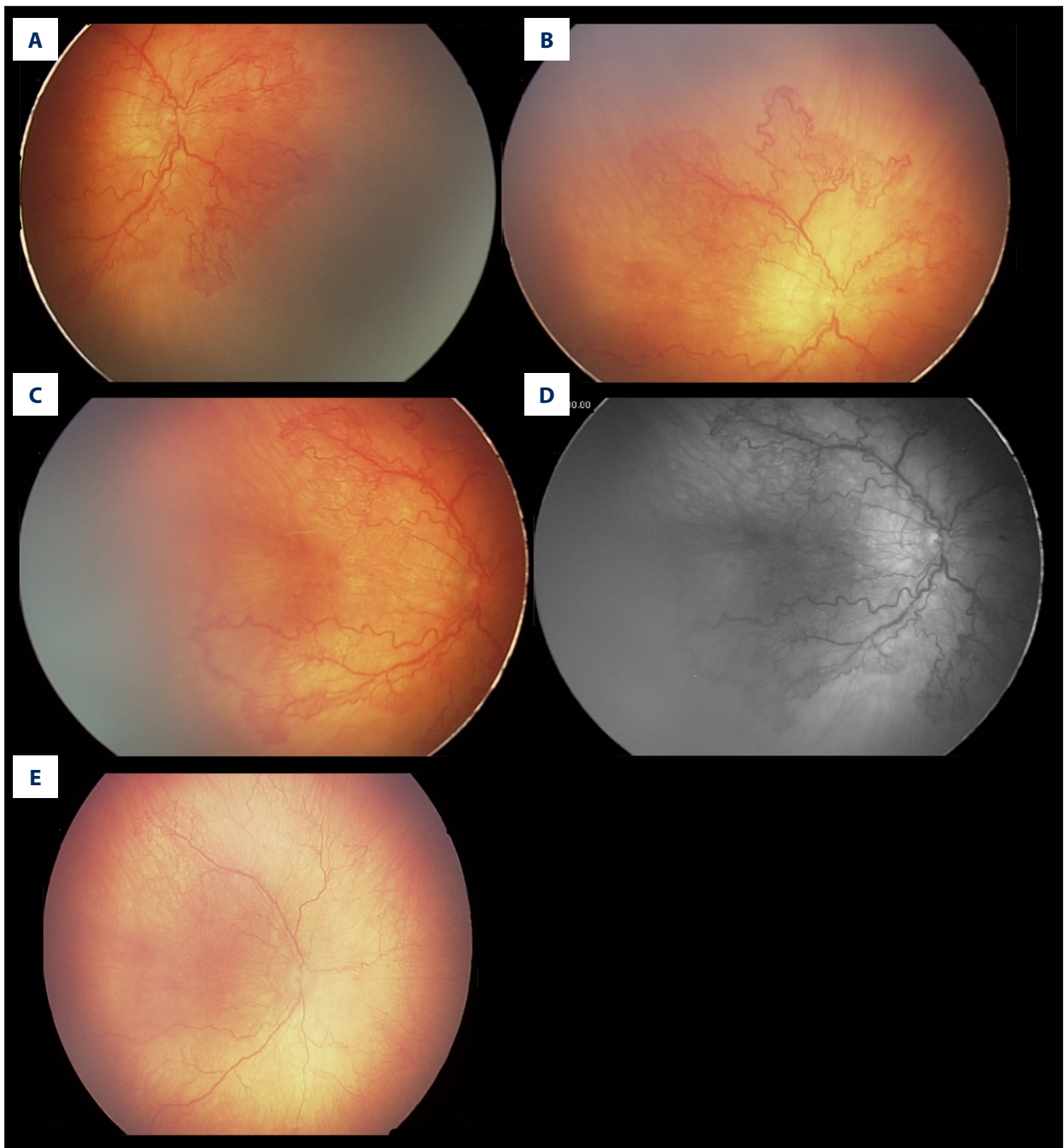
Figure 5. (**A**) RE – retinal vessels are very tortuous and form a syncytial pattern; (**B, C**) RE – arterio-venous shunts are visible, indicating that retinal vessels are not going to grow towards the periphery, the landmarks of the macular region are not individualized; (**D**) RE – the black and white image shows more precisely the length of the retinal vessels, the arterio-venous shunts and the extent of avascular retina; (**E**) RE – 5 days after IVB, the retinal vessels are significantly less tortuous and dilated and, arterio-venous shunting is less obvious.
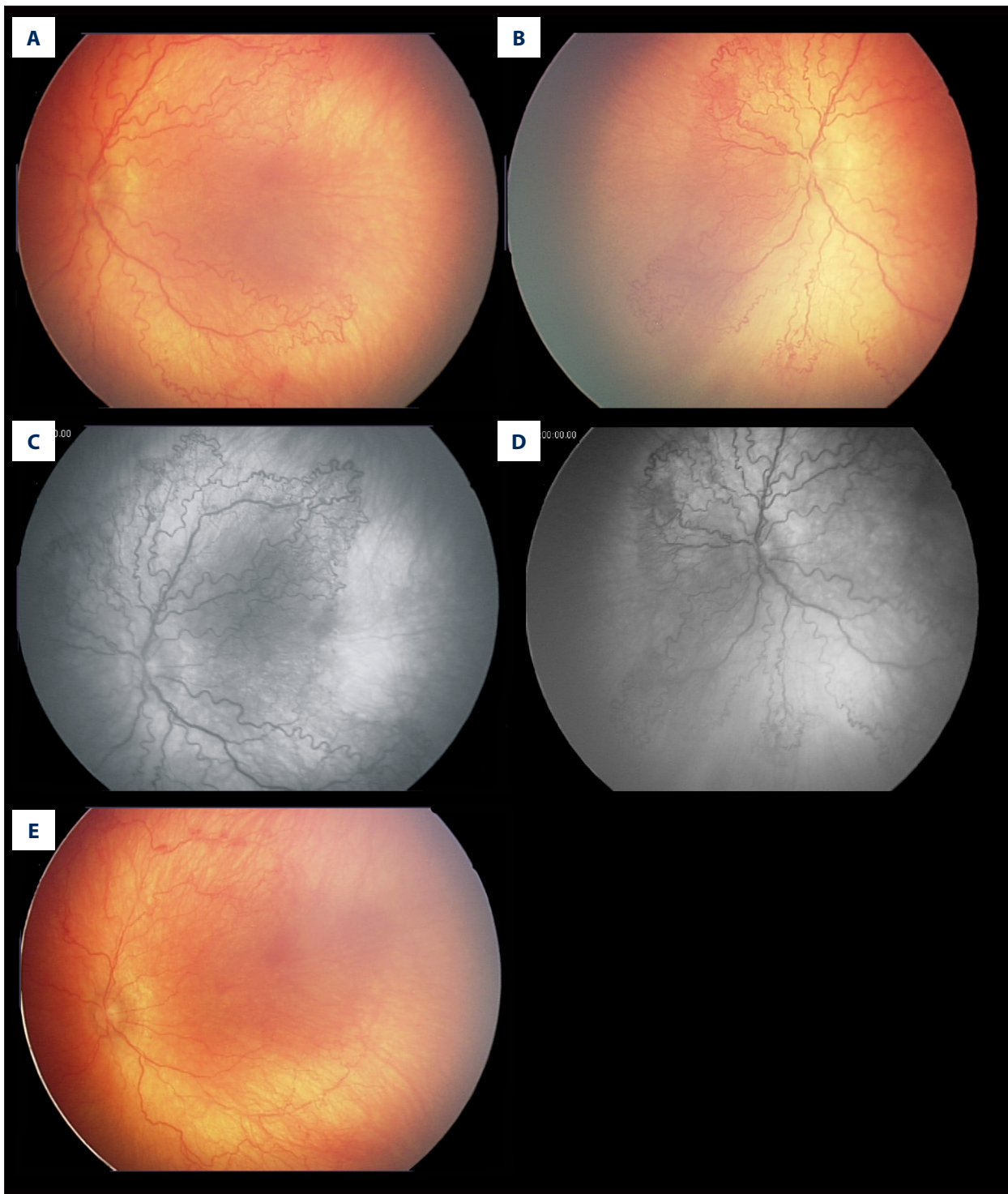
Figure 6. (**A–D**) Present the aspects in LE, which are similar to Figure 5A–5D RE. (**E**) Shows the aspect of the RE, 5 days following IVB, the retinal vessels are significantly less tortuous and dilated, arterio-venous shunting is less obvious.
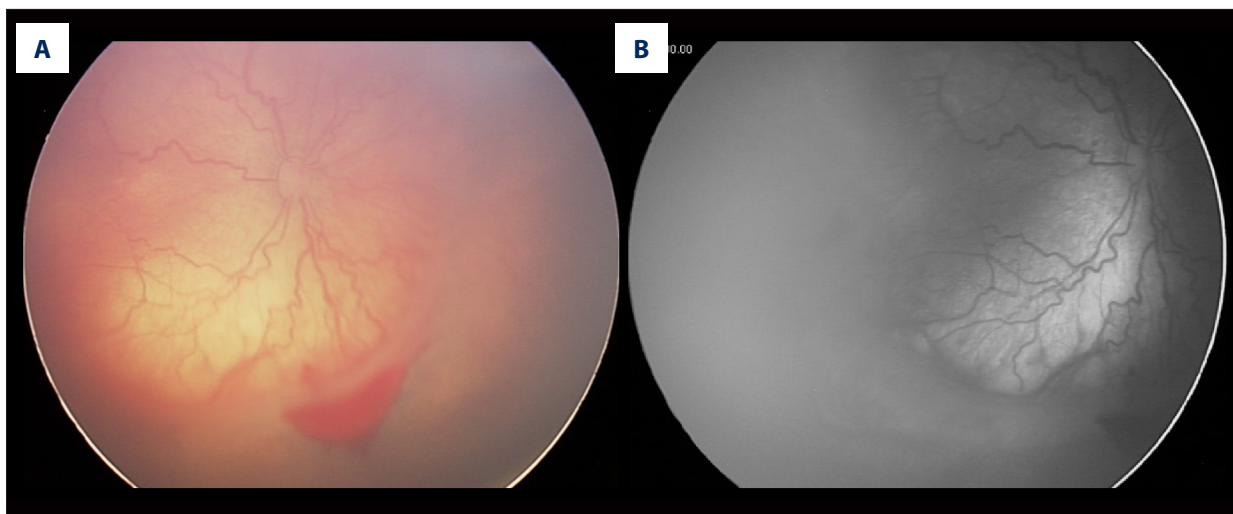
Figure 7. (A) RE – retinal vessels are more tortuous than dilated, especially the veins, inferior preretinal fibrosis, accompanied by a preretinal hemorrhage; retinal vessels are very short, a large area of non-vascularized retina is identified; **(B)** RE – preretinal fibrosis extends along the infero-temporal vascular arcade, temporal retina is avascular.

Discussion

Descriptive statistics of the study sample

According to our National Institute for Statistics, the prematurity rate in Romania is estimated around 9%, and in our region, it is around 8%. With an infantile mortality rate of 9/1000, Romania ranks first in the European Union. Prematurity is the major cause of infantile mortality in Romania.

The reasoning behind screening infants older than 31 weeks of GA in Romania is represented by the fact that in a moderate income country, different criteria for ROP screening apply, as ROP requiring treatment was identified in more mature babies [2]. For instance, the maximal GA in our series was 32 weeks, and if we had used the screening criteria of GA ≤31 weeks, this case would have been missed.

Various studies from the West and Japan describe APROP in infants <30 weeks' GA and <1000 g BW [8–10]. In a recently published study, low GA was a significant risk factor for developing any stage of ROP, and the severity of ROP was inversely related to GA and BW [11]. However, data from India show APROP in older and heavier infants [12–15]. In a recent study from north India, 15.91% infants developing APROP had a BW above 1500 g [12]. In Southwest China, screening for ROP is performed in all infants with GA <37 weeks and BW ≤2500 g [16]. In our series, 7 from the 23 prematures with APROP had GA ≥30 weeks (30.43%), 15 of them had BW ≥1000 g (65.22%) and 2 of them had BW ≥1500 g (8.70%).

Several studies reported the risk factors for zone 1 APROP: extreme prematurity, disruption of vasculogenesis and a low platelet count [9,15,17]. These factors do not explain APROP in older and heavier infants. A recent study reported the use of supplemental unblended oxygen in heavier infants developing APROP [14]. Most of the heavier and older infants in the present series had multiple comorbidities and received supplemental oxygen. Early and excessive exposure to unmonitored oxygen may lead to APROP-like morphology in these infants [18]. The small number of cases does not allow us to prove causal association of any risk factor with APROP in heavier and older infants.

One of the most critical features of APROP is its direct progression from stage 1 to stage 3 ROP. An inexperienced examiner may be confused by the absence of the extraretinal ridge. The rapid progression of APROP to stage 4 and 5 ROP justifies its previous name of „rush disease" [3,8].

We confirm one observation described by other authors regarding APROP in heavier and older babies: a preponderance of zone 2 APROP with more mature central vasculature compared with the poorly developed vasculature in zone 1 APROP [18].

Laser photocoagulation for APROP in our series

Laser became the primary modality of ROP treatment in the 1990s and it has been reported to be effective in over 90% of ROP cases [19]. However, laser is destructive and several related complications were reported: burns of the cornea, iris, and lens; hyphema; uveitis; retinal hemorrhage; and choroidal ruptures [20]. In our series we report 2 cases of mild anterior uveitis following laser photocoagulation for APROP, with prompt resolution following mydriatic and anti-inflammatory eye drops.
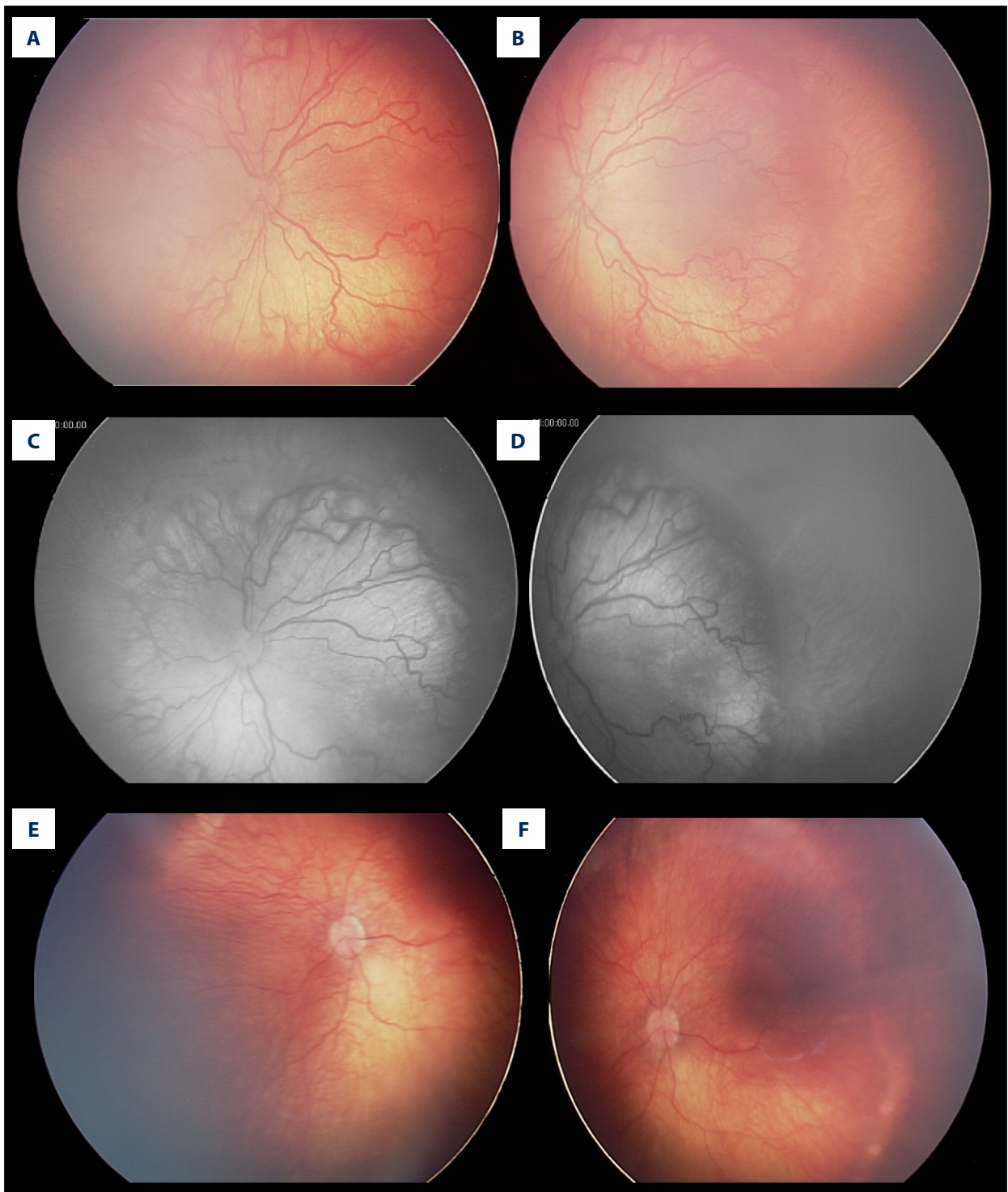
Figure 8. (**A**) LE – retinal vessels (mainly the veins) are tortuous and dilated throughout the posterior pole, arterio-venous shunting is present, no visible ridge; (**B**) LE – the temporal limit between the vascular and avascular retina is clearly visible as a highly vascularized tissue; there is no retinal traction yet; (**C**) LE – arterio-venous shunts developed between the vascular arcades; (**D**) LE – the black and white photo reveals the extent of avascular retina; (**E, F**) LE – 8 weeks from IVB, ROP regressed, retinal vessels are normal and the ancient limit between the vascularized and nonvascularized retina is identifiable (**F**).

Table 4. Regression of APROP after treatment.

Treatment	Treated eyes	Eyes with regression (%)	Eyes without regression (%)	Patients	Patients with bilateral regression (%)	Patients with unilateral regression (%)	Patients with bilateral progression (%)
Laser	12	9 (75%)	3 (25%)	6	4 (66.66%)	1 (16.66%)	1 (16.66%)
IVB	34	29 (85.29%)	5 (14.71%)	17	13 (76.47%)	3 (17.65%)	1 (5.88%)

Table 5. GA, BW, PNA and PMA variation between treatment groups and outcome.

Parameter	Outcome	IVB group		PRP group	
			Mann-Whitney U test significance		Mann-Whitney U test significance
GA (weeks)	Good	28.38	0.876	29.44	0.282
	Bad	28.00		31.00	
BW (g)	Good	1094.70	0.755	1213.33	0.864
	Bad	1095.00		1153.33	
PNA (weeks)	Good	5.69	0.432	6.67	0.100
	Bad	7.50		6.00	
PMA (weeks)	Good	34.08	0.639	36.11	0.600
	Bad	35.50		37.00	

Table 6. Advantages and disadvantages of IVB over laser in APROP.

Characteristic	Laser	IVB
Duration of treatment	Long	Very short
Difficulty of treatment	Laborious	Easy
Price	Expensive	Not expensive
Local conditions (small pupils, hazy media)	Very difficult, sometimes impossible	Normal
General condition of the infant	Sometimes risky	Not influenced
Development of retinal vascularization	Stopped	Continues
Long term effects on the eye	Possible: visual field loss, myopia	Not known
Efficacy	Significantly lower in our series	Significantly higher in our series
Local side effects	Uveitis, macular dragging	Endophthalmitis, cataract, vitreous hemorrhage (not reported so far)
Systemic safety	Safe	Questionable

Peripheral retina is photocoagulated in order to preserve the central vision [19] and long-term visual loss can be associated with it [21]. Laser photocoagulation does not address the underlying cause of the disease [19]. Ablation of the nonvascularized retina, according to ETROP criteria, reduces blindness, but many patients do not achieve good visual acuity [19]. Ideally, the reduction of risk factors that interfere with normal retinal vascularization is more likely to be more effective than late treatment of neovascularization [19].

Zone I APROP is known to have worse prognosis following laser photocoagulation, compared with the classical form of the disease. Unfavorable outcome rates varying between 55.2% and 100% were reported in the literature [5,22–26].

We reported the number of laser burns that were registered on the laser console, but not all of them were effective on the retina. This explains the extremely high number of laser burns (maximum 6000 per eye) in our series.

Laser photocoagulation of the avascular retina beneath the flat stage 3 ROP is difficult and often untreated avascular retina remains a source of VEGF, continuing to drive the ROP process. Therefore, in most APROP cases, 1 laser session is not enough to stop the progression of the disease. APROP may regress after the laser session, but it can reactivate. Reactivation is characterized by the return of plus disease, progressive contraction of the posterior hyaloid and posterior traction retinal detachment [8].

The main reason for insufficient initial laser treatment was represented by the absence of landmarks between the vascularized and non-vascularized retina towards the posterior pole at the moment of the first laser session. These landmarks became visible by the moment of the second laser session, allowing us to complete the treatment.

We identified macular dragging in 1 of our 6 APROP patients within the laser photocoagulation group (16.66%). This condition prevents the normal macular development by displacing the macula [27].

IVB for APROP in our series

VEGF immunoreactivity is increased in the vascularized regions of fibrovascular membranes, as proved by a study that investigated vitreous samples taken during vitrectomy for stage 5 ROP [28]. This evidence stands in favor of the anti-VEGF treatment in ROP.

APROP regressed following IVB, in 29 of the 34 eyes, in our series (85.29%). Adding laser photocoagulation of the retina in 3 of the 5 eyes with poor outcome led to the salvation of all the 3 eyes. Fortunately, the 2 eyes with poor outcome did not belong to the same infant.

We report no local complications related to IVB in our series. Several studies reported late reactivation following IVB [29–33]. With a follow up ranging from 80–144 weeks from treatment, we did not observe any late reactivation of APROP, following IVB, in our series.

In stages 4 and 5 ROP, IVB is contraindicated, as it accelerates the progression of retinal detachment [34].

IVB versus laser photocoagulation in the treatment of APROP

VEGF and ROP

The role of VEGF in the neovascularization and vascular permeability associated with ROP was proved. VEGF is the main chemical mediator responsible for the vascular abnormalities and the fibrovascular proliferation in ROP [35]. Therefore, the goal of therapy for ROP is to decrease VEGF, either by ablating the nonvascularized retina that produces VEGF (LASER therapy) or by inactivating the VEGF (anti-VEGF therapy) [36]. Bevacizumab is a humanized recombinant full antibody that inhibits the biological activity of VEGF. It is widely used in ophthalmology, off-label, in the treatment of neovascular proliferative diseases: age-related macular degeneration, diabetic retinopathy, neovascular glaucoma [36], and, more recently, in choroidal metastases [37].

Laser photocoagulation of the retina acts by destroying the cellular elements producing VEGF. However, the VEGF in the vitreous cavity and in the subretinal fluid continues to act, despite timely and complete destruction of its source. This explains the failures after laser in ROP. Therefore, the use of anti-VEGF medication as an alternative for the treatment of ROP appears logical [38,39].

Difficulties that drove us to change the treatment modality

In a previous study, we reported a significantly lower success rate following laser photocoagulation for APROP, compared with all ROP laser-treated cases: 53.84% versus 88.12% [27]. This was our first reason to switch from laser photocoagulation to IVB in APROP. In addition to this, in APROP, the laser sessions were long, laborious, and often needed to be repeated, because at the moment of treatment, the limit between the vascularized and nonvascularized retina was not clearly visible, especially toward the posterior pole. Local conditions, such as poor pupil dilation, the persistence of the pupillary membrane, and the association of some vitreous hemorrhage, prevented us from performing adequate laser therapy in APROP. Sometimes, the general condition of the infant was put at risk by the long anesthesia time required for the complete laser treatment and forced us to conclude the treatment, before the full ablation of the nonvascularized retina. Another important reason for our change from laser photocoagulation to IVB was the lack of destruction to the retina resulting from bevacizumab therapy, compared with laser ablative therapy.

Comparative anatomical outcomes of IVB and laser photocoagulation

APROP regression rate was significantly better after IVB compared with laser photocoagulation in our series. In a study published this year, the authors report similar regression rates with IVB and with laser photocoagulation, but the study included all ROP cases, not only the APROP ones [40]. In another published study, the authors found higher ROP recurrence rate after IVB, compared with laser photocoagulation, but they identified a higher occurrence rate of macular ectopia in the laser photocoagulation-treated eyes, compared with the IVB-treated eyes [41]. In our series, we found macular ectopia only in the laser photocoagulation-treated eyes (16.66%).

We previously reported the observation that, unlike with laser, the retinal vascularization continued after the intravitreal injection of bevacizumab [7]. Within the IVB-treated group, in all 29 eyes with APROP regression, the retinal vessels developed up to the retinal periphery.

The explanation for the quicker response to IVB, compared with laser photocoagulation, resides in the different mechanisms of action of the 2 methods: laser photocoagulation of the retina destroys the source of VEGF, whereas the existing VEGF continues to act; IVB annihilates both VEGF production and VEGF already present in the vitreous.

In the infants within this series, we identified the bad anatomical outcome, 1 week after the initial treatment. Therefore, we consider these cases to be unresponsiveness of APROP to treatment, rather than APROP recurrence. We identified no late recurrence, neither in the laser photocoagulation group, nor in the IVB group.

Individual factors associated with outcome (characteristics of infants)

Within the 2 groups, we could not individualize any characteristics of the infants who did not respond to treatment (Table 5). It is well known that lower GA and BW are associated with worse prognosis of ROP [1,3,42]. In both groups (laser photocoagulation and IVB), infants with bad outcome did not have lower GA or BW than the ones with favorable outcome. Timely recognition and treatment are essential for the ROP outcome [4]. Timing is essential for the good response of ROP to treatment. The critical period during which ROP may have to be treated is between 34 and 37 weeks' PMA [4,43]. PMA at treatment was not significantly associated with the outcome in either of the 2 groups. Thus, within the laser group, the mean PMA at treatment in infants with good outcome was 36.11 weeks and in infants with bad outcome, 37 weeks, a difference that is not significant (P=0.600). Within

the IVB group, even if the mean PMA at treatment in infants with good outcome was lower than in infants with bad outcome (34.08 weeks versus 35.50 weeks), the difference is not statistically significant (P=0.639).

Asymmetric response to treatment

In 1 of the 6 cases within the laser photocoagulation group (16.66%) and in 3 of the 17 cases within the IVB group (17.64%), the response to treatment was asymmetric: APROP regressed in one eye and progressed in the other one. This is partly explained by the unequal development of the eye, which is also at the origin of the rare situations of unilateral ROP described in the literature [44]. Asymmetry in presentation does not explain all the asymmetric results after treatment in our series. We identified it in 2 of the 4 cases, in which the disease was more severe in the eye that had a bad outcome (1 case in each group). Another explanation is the asymmetric treatment. Within the laser group, the ablation of the nonvascularized retina in APROP required the application of many burns in both eyes, in one session, which is laborious and sometimes limited by the poor general condition of the infant that imposed treatment conclusion. Under these circumstances, the treatment may not have been sufficient in the eyes with APROP progression. Within the IVB group, we can only suppose that, given the fact that a very small volume of substance must be injected into the vitreous, we may have failed to administer the required dosage in the eyes with unfavorable outcome.

Safety issues of anti-VEGF therapy

The main issue of IVB is not efficacy, but rather safety. After intravitreal injection, anti-VEGF is found in the systemic circulation and the VEGF serum levels decrease [45,46]. In the eyes with ROP, there is a breakdown of the blood-retinal barrier, which facilitates the exit of anti-VEGF into the systemic circulation, with subsequent reduction of VEGF serum level [46]. At the moment of anti-VEGF injection, the infant is still in the process of organogenesis and VEGF is necessary for the development of the brain, lungs, kidneys, and skeleton [47]. Therefore, possible adverse effects on VEGF-dependent development must be considered: normal angiogenesis, regulation of vascular permeability, endothelial differentiation during fetal brain development, signaling between major neural cells, maintenance, and development of the blood-retinal barrier [47]. Systemic side effects are difficult to assess, as the infants with ROP present developmental disorders more often than other infants [48]. In the BEAT-ROP study, 5 of the 7 deaths were in the bevacizumab group, from respiratory disease. The 2 deaths in the laser group were caused by sepsis and respiratory disease, respectively [6]. In a retrospective meta-analysis of systemic side effects of bevacizumab, 585 patients included in different studies were analyzed. Systemic

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complications were reported in 8 cases after IVB (1.36%). However, in none of them was the anti-VEGF therapy considered to be the cause of the complication [49]. In a case-control study, 1 infant died after IVB [50]. In another study, 1 infant showed delay in growth, pulmonary dysplasia, and intraventricular hemorrhage [51]. After unilateral injection in 1 patient, the vascular activity decreased in the patient's other eye [52]. There was 1 report of short-term raised liver enzymes after bevacizumab injection [53].

The few selected studies designed to evaluate specific abnormalities detected no systemic complications [51,54,55]. In order to definitely determine an increase in mortality related to IVB, compared with laser treatment for ROP, approximately 2800 infants are needed [6]. To minimize the systemic risks, a minimal effective dose of an anti-VEGF agent with a rapid systemic clearance is recommended [47]. In our series, we used half of the bevacizumab dose for adults (0.625 mg/eye), but there is not enough evidence to support a recommended dosage [49].

According to these data, concern remains about systemic toxicity of intravitreal anti-VEGF therapy in infants.

In the eye, VEGF also plays the role of a neural survival factor and, therefore, its suppression is suspected to interfere with the normal development of neural retinal components [47]. However, this supposition was not confirmed by the histopathological studies performed in animals and in a very premature infant [56,57].

Advantages and disadvantages of IVB

Bevacizumab administered intravitreally has the following advantages over laser photocoagulation of the retina: it is shorter, less destructive, easier, less expensive, accessible; it can be performed in eyes with small pupils and hazy media and in infants in poor general health, and it allows the continuation of retinal vascularization toward the periphery [50,58]. IVB eliminates the direct effects of laser, which may include retinal atrophy with secondary visual field loss and scleral weakening that leads to myopia [59]. The possible local complications related to IVB are lens injury, retinal detachment, and

infection; but no reports of these have appeared in the literature so far, in relation to IVB for ROP. A histopathological study performed 20 weeks after the intravitreal injection of bevacizumab in humans showed no signs of toxic effects, including inflammation, degeneration, or necrosis [56].

In our experience, one of the main advantages of IVB is its short duration of treatment. This becomes highly important if there is not enough time for general anesthesia and laser photocoagulation could not be performed, due to the bad health condition of the infant. The only concerns are related to the systemic safety issues of IVB, which are not completely resolved. The comparative advantages and disadvantages of IVB and laser photocoagulation for APROP are synthesized in Table 6. As many other authors, we believe that currently, intravitreal anti-VEGF injections represent the best therapeutic approach for APROP, even if the systemic safety issues and consequences of this treatment were not fully addressed [60].

Conclusions

In our series, we found a statistically significantly higher APROP regression rate after IVB, as compared with laser photocoagulation. Compared with laser photocoagulation, IVB is easier, more accessible, and less expensive; has a shorter duration; and can be performed if the pupils are small and the media are hazy. IVB's short duration of treatment becomes a valuable asset if the patient's poor health will not allow enough time for general anesthesia for laser photocoagulation.

Consequently, in our practice, IVB has replaced laser photocoagulation in APROP, becoming the standard of care in this severe form of ROP.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References:

1. Stenkuller PG, Du L, Gilbert C et al: Childhood blindness. J AAPOS, 1999; 3: 26–32

2. Gilbert C, Fielder A, Gordillo L et al: International NO-ROP Group. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs. Pediatrics, 2005; 115(5): e518–25

3. Clark D, Mandal K: Treatment of retinopathy of prematurity. Early Hum Dev, 2008; 84: 95–99

4. Good WV, Carden SM: Retinopathy of prematurity. Br J Ophthalmol, 2006; 90: 254–55

5. Early Treatment for Retinopathy of Prematurity Cooperative Group: Revised indication for the treatment of retinopathy of prematurity: Results of early treatment for ROP randomized trial. Arch Ophthalmol, 2003; 121: 1684–96

6. Mintz-Hittner HA, Kennedy KA, Chuang AZ: Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med, 2011; 364: 603–15

7. Nicoară SD, Nascutzy C, Cristian C et al: Outcomes and prognostic factors of intravitreal bevacizumab monotherapy in zone I stage 3+ and aggressive posterior retinopathy of premaaturity. J Ophthalmol, 2015; 2015: 102582

8. Drenser KA, Trese MT, Capone A Jr: Aggressive posterior retinopathy of prematurity. Retina, 2010; 30 (4 Suppl.): 37–40

9. International committee for the classification of retinopathy of prematurity: The international classification of retinopathy of prematurity revisited. Arch Ophthalmol, 2005; 123: 991–99

10. Azuma N, Ishikawa K, Hama Y et al: Early vitreous surgery for aggressive posterior retinopathy of prematurity. Am J Ophthalmol, 2006; 142: 636–43

11. Celebi ARC, Petricli IS, Hekimoglu E et al: The incidence and risk factors of severe retinopathy of prematurity in extremely low birth weight infants in Turkey. Med Sci Monit, 2014; 20: 1647–53

12. Sanghi G, Dogra MR, Das P et al: Aggressive posterior retinopathy of prematurity in Asian Indian babies: Spectrum of disease and outcome after laser treatment. Retina, 2009; 29: 1335–39

13. Jalali S, Kesarwani S, Hussain A: Outcomes of a protocol-based management for zone 1retinopathy of prematurity: The Indian Twin Cities ROP screening program report number. Am J Ophthalmol, 2011; 151: 719–24

14. Shah PK, Narendran V, Kalpana N: Aggressive posterior retinopathy of prematurity in large preterm babies in South India. Arch Dis Child Fetal Neonatal Ed, 2012; 97: F371–75

15. Vinekar A, Hegde K, Gilbert C et al: Do platelets have a role in the pathogenesis of aggressive posterior retinopathy of prematurity? Retina, 2010; 30: S20–23

16. Liu Q, Yin ZQ, Ke N et al: Incidence of retinopathy of prematurity in southwestern China and analysis of risk factors. Med Sci Monit, 2014; 20: 1442–51

17. Flynn JT, Chan-Ling T: Retinopathy of prematurity: Two distinct mechanisms that underlie zone1 and zone 2 disease. Am J Ophthalmol, 2006; 142: 46–59

18. Sanghi G, Dogra MR, Katoch D, Gupta A: Aggressive posterior retinopathy of prematurity in infants ≥1500 g birth weight. Indian J Ophthalmol, 2014; 62: 254–57

19. Hellström A, Smith LE, Dammann O: Retinopathy of prematurity. Lancet, 2013; 382: 1445–57

20. Laser ROP Study Group: Laser therapy for retinopathy of prematurity. Arch Ophthalmol, 1994; 112 (2): 154–56

21. Mataftsi A, Dimitrakos SA, Adams GGW: Mediators involved in retinopathy of prematurity and emerging therapeutic targets. Early Hum Dev, 2011; 87: 683–90

22. Cryotherapy for Retinopathy of Prematurity Cooperative Group: Multicenter trial of cryotherapy for retinopathy of prematurity. Three-month outcome. Arch Ophthalmol, 1990; 108: 195–204

23. Flynn JT, Chan-Ling T: Retinopathy of prematurity: Two distinct mechanisms that underlie zone 1 and zone 2 disease. Am J Ophthalmol, 2006; 142: 46–59

24. Katz X, Kychenthal A, Dorta P: Zone I retinopathy of prematurity. J AAPOS, 2000; 4: 373–76

25. O'Keefe M, Lanigan B, Long VW: Outcome of zone I retinopathy of prematurity. Acta Ophthalmol Scand, 2003; 81: 614–16

26. Kychenthal A, Dorta P, Katz X: Zone I retinopathy of prematurity: Clinical characteristics and treatment outcomes. Retina, 2006; 26: S11–15

27. Nicoara SD, Cristian C, Irimescu I et al: Diode laser photocoagulaiton for retinopathy of prematurity: Outcomes after 7 years of treatment. J Pediatr Ophthalmol Strabismus, 2014; 51(1): 39–45

28. Umeda N, Ozaki H, Hayashi H: Colocalization of Tie2, angiopoietin 2 and vascular endothelial growth factor in fibrovascular membrane from patients with retinopathy of prematurity. Ophthalm Res, 2003; 35: 217–23

29. Jang SY, Choi KS, Lee SJ: Delayed-onset retinal detachment after an intravitreal injection of ranibizumab for zone 1 plus retinopathy of prematurity. J AAPOS, 2010; 14: 457–59

30. Lee BJ, Kim JH, Yu YS: Delayed onset atypical vitreoretinal traction band formation after an intravitreal injection of bevacizumab in stage 3 retinopathy of prematurity. Eye, 2012; 26: 903–10

31. Patel RD, Blair MP, Shapiro MJ, Lichtenstein SJ: Significant treatment failure with intravitreous bevacizumab for retinopathy of prematurity. Arch Ophthalmol, 2012; 130: 801–2

32. Hu J, Blair MP, Shapiro MJ et al: Reactivation of retinopathy of prematurity after bevacizumab injection. Arch Ophthalmol, 2012; 130: 1000–6

33. Ittiara S, Blair MP, Shapiro MJ, Lichtenstein SJ: Exudative retinopathy and detachment: A late reactivation of retinopathy of prematurity after intravitreal bevacizumab. J AAPOS, 2013; 17: 323–25

34. Alba LE, Zaldua RA, Masini RA: [Off-label use of intravitreal bevacizumab for severe retinopathy of prematurity.] Arch Soc Esp Oftalmol, 2015; 90(2): 81–86 [in Spanish]

35. Smith LE: Pathogenesis of retinopathy of prematurity. Growth Horm IGF Res, 2004; 14: S140–44

36. Niranjan HS, Benakappa N, Bharath KR, Kamath VM: Retinopathy of prematurity –promising newer modalities of treatment. Indian Pediatr, 2012; 49: 139–43

37. Yasui H, Sato K, Takeyama Y et al: Effective treatment with intravitreal injection with bevacizumab for exudative retinal detachment secondary to choroidal metastasis of non-small cell lung carcinoma. Am J Case Rep, 2015; 16: 728–32

38. Sonmez K, Drenser KA, Capone A Jr, Trese MT: Vitreous levels of stromal cell-derived factor 1 and vascular endothelial growth factor in patients with retinopathy of prematurity. Ophthalmology, 2008; 115: 1065–70

39. Lashkari K, Hirose T, Yazdany J et al: Vascular endothelial growth factor and hepatocyte growth factor levels are differentially elevated in patients with advanced retinopathy of prematurity. Am J Pathol, 2000; 156: 1337–44

40. Maram I, Kamiar M, Nasrin T: Treatment of type 1 retinopathy of prematurity with bevacizumab versus laser. JAAPOS, 2015; 19: 140–44

41. Hwang KC, Hubbard GB, Hutchinson AK, Lambert SR: Outcomes after intravitreal bevacizumab versus laser photocoagulation for retinopathy of prematurity: a 5-year retrospective analysis. Ophthalmology, 2015; 122: 1008–15

42. Coats DK, Miller AM, Hussein MAW et al: Involution of retinopathy of prematurity after laser treatment: Factors associated with development of retinal detachment. Am J Ophthalmol, 2005; 140: 214–22

43. Kieselbach GF, Ramharter A, Baldissera I, Kralinger MT: Laser photocoagulaiton for retinopathy of prematurity: Structural and funcitonal outcome. Acta Ophthalmol Scand, 2006; 84: 21–26

44. Mushawiahti M, Rokiah O, Umi KMN, Leow SN: Long term outcome in unilaterally treated retinopathy of prematurity: A case report, Med Health, 2014; 9(2): 134–38

45. Wang D, Choi CS, LeeSJ: Serum concentration of vascular endothelial growth factor after bilateral intravitreal injection of bevacizumab. Korean J Ophthalmol, 2014; 28(1): 32–38

46. Cameiro AM, Costa R, Falcao MS et al: Vascular endothelial growth factor plasma levels before and after treatment of neovascular age-related macular degeneration with bevacizumab or ranibizumab. Acta Ophthalmol, 2012; 90(1): e25–30

47. Yang CH: Anti-vascular endothelium growth factor therapy for retinopathy of prematurity: A continuing debate. Taiwan Journal of Ophthalmology, 2012; 2(4): 115–16

48. Hartnett ME, Penn JS: Mechanisms and management of retinopathy of prematurity. N Engl J Med, 2012; 367(26): 2515–26

49. Pertl L, Steinwender G, Mayer C et al: A systematic review and meta-analysis on the safety of Vascular Endothelial Growth Factor (VEGF) inhibitors for the treatment of retinopathy of prematurity. PLoS One, 2015; 10(6): e0129383

50. Lepore D, Quinn GE, Molle F et al: Intravitreal bevacizumab versus laser treatment in type 1 retinopathy of prematurity: Report on fluorescein angiografic findings. Ophthalmology, 2014; 121(11): 2212–19

51. Martinez-Castellanos MA, Schwartz S, Hernandez-Rojas ML et al: Long-term effect of anti-angiogenic therapy for retinopathy of prematurity up to 5 years of follow up. Retina, 2013; 33(2): 329–38

52. Sahin A, Sahin M, Cingu AC et al: Intravitreal bevacizumab monotherapy for retinopathy of prematurity. Pediatr Int, 2013; 55(5): 599–603

53. Jalali S, Balakinshnan D, Zeynalova Z et al: Serious adverse events and visual outcomes of rescue therapy using adjunct bevacizumab to laser and surgery for retinopathy of prematurity. The Indian Twin Cities ROP screening program report number 5. Arch Dis Child Fetal Neonatol Ed, 2013; 98(4): F327–33

54. Moran S, O'Keefe M, Hartnett C et al: Bevacizumab versus diode laser in stage 3 posterior retinopathy of prematurity. Acta Ophthalmol, 2014; 92(6): e496–97

55. Araz-Ersan B, Kir N, Tuncer S et al: Preliminary anatomical and neurodevelopmental outcomes of intravitreal bevacizumab as adjunctive treatment for retinopah of prematurity. Curr Eye Res, 2014; 15(7): 1–7

56. Kong L, Mintz-Hittner HA, Penland RL et al: Intravitreous bevacizumab as anti-vascular endothelial growth factor therapy for retinopathy of prematurity: A morphologic study. Arch Ophthalmol, 2008; 126: 1161–63

57. Axel-Siegel R, Herscovici Z, Hasanreisoglu M et al: Effect of intravitreal bevacizumab (Avastin) on the growing rabbit eye. Curr Eye Res, 2009; 34(8): 660–65

58. Kuniyosh K, Sugioka K, Sakuramoto H et al: Intravitreal injection of bevacizumab for retinopathy of prematurity. Jpn J Ophthalmol, 2014; 58: 237–43

59. Wong RK, Warden SM, Lee TC, Chan RVP: Review and case discussion: Aggressive posterior retinopathy of prematurity. Retinal Physician, 2008; 9: 1–2

60. Lorenz B, Stieger K: Retinopathy of prematurity: Recent developments in diagnosis and treatment. Expert Review of Ophthalmology, 2015; 10(2): 1–16