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Original article

Neonatal risk factors for the development of aggressive retinopathy of prematurity (A-ROP) and anti-VEGF treatment outcomes

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Summary

Introduction. Retinopathy of prematurity (ROP) is a neurovascular disease that, if left untreated, leads to severe visual impairment and blindness. Early diagnosis and timely therapy reduce the risk of a severe outcome. The most significant risk factors for the development of the disease are low gestational age, low birth weight, development of respiratory distress and prolonged need for oxygen therapy, neonatal sepsis, anaemia, and others. This paper analyses the most significant risk factors and the outcome of treatment with anti-VEGF therapy, as well as the additional need for laser photocoagulation.

Methods. A retrospective study was conducted involving 30 children (60 eyes) with the A-ROP form of retinopathy, divided into two groups according to the anti-VEGF agent administered (bevacizumab or ranibizumab).

Results. Regarding gestational age, a statistically significant difference was found between the two groups. Birth weight was higher in the group that received intravitreal bevacizumab (IVB). Readministration of the drug was required in three patients (five eyes) treated with bevacizumab, and in four patients (nine eyes) who received ranibizumab (IVR). The need for laser photocoagulation was 40% in the IVB group versus 100% in the IVR group, a statistically highly significant difference.

Conclusion. Timely diagnosis and adequate therapy significantly improve outcomes and reduce the risk of severe visual impairment. In this study, bevacizumab showed superiority over ranibizumab with respect to the effect on ROP reactivation and the need for additional laser intervention.

Key words: ROP, retinopathy of prematurity, anti-VEGF, bevacizumab, ranibizumab

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Introduction

Retinopathy of prematurity (ROP) is a neurovascular disease that, if left untreated, leads to severe visual impairment and blindness. Early diagnosis and timely therapy reduce the risk of a severe outcome. The main risk factor for the development of the disease is premature birth. As neonatal survival continues to improve due to advances in perinatal and neonatal care, especially in underdeveloped and developing countries, the incidence and recognition of ROP have significantly increased. ROP represents a unique interaction of systemic immaturity, disrupted development of retinal blood vessels, and exposure to environmental risk factors, primarily oxygen therapy. This condition highlights the importance of timely screening, diagnosis, and intervention to prevent lifelong visual impairment [1].

Preterm birth is common worldwide. In addition to increased mortality, short and longterm complications resulting from arrested normal development after preterm birth include retinopathy of prematurity (ROP), as well as delayed physical growth, vascular abnormalities (including intraventricular haemorrhage), pulmonary disease, sepsis, poor neurocognitive development, and metabolic dysregulation with an increased risk of diabetes in young adulthood. In humans, the development of the retinal vascular system begins in the second trimester of pregnancy and is completed around term. In infants born extremely preterm, before 28 weeks of gestation, the retina is incompletely vascularized at birth. The lower the gestational age (GA) at birth, the less developed the neural retina and the larger the area of peripheral avascularity [2].

Stages of the disease

1. **Acute disease stages** (Stages 1–3): defined by the appearance of a structure at the vascular-avascular junction as Stage 1 (demarcation line), Stage 2 (ridge), and Stage 3 (extraretinal neovascular proliferation or flat neovascularization). If more than one stage of ROP is present in the same eye, the eye is classified according to the most severe stage.

   Aggressive ROP (A-ROP): the term aggressiveposterior ROP (APROP) was previously used to describe a severe, rapidly progressive form of ROP found in the posterior Zone I or Zone II. Because of the growing recognition that this can occur outside the posterior retina and in larger preterm infants, especially in resourcelimited regions of the world, the Committee recommends the new term A-ROP.
2. **Retinal detachment (Stages 4–5)**

   a. Stages of retinal detachment are defined as Stage 4 (partial: 4A with fovea attached, 4B with foveal detachment) and Stage 5 (total).

   b. Definition of Stage 5 subcategories: Stage 5A, in which the optic disc is visible by ophthalmoscopy (indicating openfunnel detachment); Stage 5B, in which the optic disc is not visible because of retrolental fibrovascular tissue or closedfunnel detachment; and Stage 5C, in which Stage 5B is accompanied by anterior segment changes (e.g., marked shallowing of the anterior chamber, iridocorneolenticular adhesions, corneal opacification), indicating a closedfunnel configuration [3].

Treatment

In the United States, the BEATROP study investigators demonstrated benefit in infants with zone I disease, but less so for zone II. The BEATROP study indicated a benefit of bevacizumab over laser in some ROP cases, particularly in infants with zone I disease. The multicenter, randomized, openlabel RAINBOW study found that ranibizumab may be superior to laser with fewer adverse structural ophthalmic outcomes. A third anti-VEGF antibody, aflibercept, showed an 85% success rate in a multicenter, randomized trial, with laser

treatment having similarly high success rates of 82% [4].

This study aimed to determine the most significant risk factors for the development of ROP and the treatment outcomes of bevacizumab versus ranibizumab, as reflected by the need for additional laser treatment.

Methods

A retrospective comparative study was conducted involving 30 children (60 eyes) with A-ROP who were treated at the Centre for Neonatology of the Institute for Child Diseases, Clinical Centre of Montenegro, between January 2022 and March 2024. The main inclusion criterion was the presence of aggressive ROP (A-ROP). Examination was performed after adequate patient preparation with instillation of tropicamide 0.5% and phenylephrine 2.5% three times at 15minute intervals, after achieving adequate mydriasis. The examination was performed using an indirect ophthalmoscope and a 20 D lens with a blepharostat and indentor. Fundus findings were documented using a RetCam3 (Natus) device. After the diagnosis was established, informed parental consent and approval for intravitreal injection in both eyes were obtained. Patients were divided into two groups according to the anti-VEGF agent administered (bevacizumab 0.625 mg [0.025 ml] and ranibizumab 0.2 mg [0.02 ml]). After the intervention, patients were examined on days 1, 7, 14, and 21, and then every two weeks for the following three months. Thereafter, repeat intravitreal drug administration or laser intervention was performed according to the clinical findings.

Results

Regarding gestational age, a statistically significant difference (*p* = 0.039) was found between the two groups. Birth weight was higher in the group that received intravitreal bevacizumab (IVB).

Analysis of birth weight and its influence on the development of A-ROP revealed a statistically significant difference in birth weight (*p* < 0.05), with the mean birth weight being lower in the group that received ranibizumab compared to the group that received bevacizumab.

The one-minute Apgar score was analyzed and showed no statistically significant difference (*p* = 0.66) between the two groups.

Table 1. Gestational age (weeks)

Drug	N	Mean	SD	Median	Min	Max
Bevacizumab	15	30.3	2.5	32	26	33
Ranibizumab	15	28.5	2.1	28	26	32

Table 2. Birth weight (grams)

Drug	N	Mean	SD	Median	Min	Max
Bevacizumab	15	1510.7	364.8	1530	860	2000
Ranibizumab	15	1205.3	392.6	1060	550	1880

Table 3. Need for laser photocoagulation

Drug	Laser	No laser	Total
Bevacizumab	6 (40%)	9 (60%)	15
Ranibizumab	15 (100%)	0 (0%)	15

Readministration of the drug was required in 3/15 patients (five eyes) treated with bevacizumab (20%), and in 4/15 patients (nine eyes) who received ranibizumab (26.7%). The need for laser photocoagulation was 40% in the IVB group versus 100% in the IVR group, a statistically highly significant difference (Fisher's exact test, *p* = 0.0007).

Discussion

This study analyzed the treatment outcomes of aggressive retinopathy of prematurity (A-ROP) with intravitreal bevacizumab and ranibizumab, with particular emphasis on neonatal factors and the need for additional therapeutic procedures. The results indicate certain differences between the groups that may have clinical significance.

Analysis of gestational age revealed a statistically significant difference (*p* = 0.039) between the groups, with infants treated with bevacizumab having a higher mean gestational age compared to the group treated with ranibizumab. It is well known that lower gestational age and lower birth weight are among the most important risk factors for the development of severe forms of retinopathy of prematurity, including A-ROP. Therefore, it can be assumed that the ranibizumabtreated group represented a more vulnerable population with a more severe initial clinical presentation and a higher risk of disease progression.

The oneminute Apgar score did not show a statistically significant difference between the groups, indicating that the immediate postnatal condition of the newborns probably did not significantly influence treatment outcomes.

Regarding treatment efficacy, the results showed that readministration of the drug was required in both groups, but somewhat more frequently in patients treated with ranibizumab (4/15, 26.7%) compared to those treated with bevacizumab (3/15, 20%). The higher number of eyes requiring repeat injection in the IVR group may be explained by the shorter intravitreal and systemic halflife of ranibizumab, potentially leading to earlier disease reactivation. These findings are consistent with literature data indicating that after ranibizumab administration, additional treatment or more careful longterm followup is more often required because of the possibility of disease relapse.

The most significant result of this study concerns the need for laser photocoagulation. In the bevacizumabtreated group, additional laser therapy was required in 40% of subjects, while all patients treated with ranibizumab required laser photocoagulation. This difference was statistically highly significant (Fisher's exact test, *p* = 0.0007), indicating greater longterm efficacy of bevacizumab in controlling A-ROP. A possible explanation for this finding is the longer duration of action of bevacizumab and stronger VEGF suppression, achieving more stable regression of neovascularization. On the other hand, although ranibizumab has the advantage of lower systemic exposure and potentially less impact on the development of other organs in premature infants, its shorter activity may account for the more frequent need for additional interventions.

Nevertheless, the results should be interpreted with certain study limitations. First, the number of subjects was relatively small, which may affect the statistical power of the study. Moreover, differences in gestational age and birth weight between the groups may represent confounding factors affecting therapeutic response. Additionally, masked patient allocation was not used. Future studies with larger sample sizes and randomized designs could provide more precise data on the comparative efficacy and safety of anti-VEGF therapy in the treatment of A-ROP.

Based on the results of this study, it can be concluded that both anti-VEGF agents demonstrated efficacy in treating A-ROP, but bevacizumab was associated with a lower need for additional laser photocoagulation and a smaller number of readministrations,

which may indicate a more stable therapeutic effect compared to ranibizumab.

Timely diagnosis and adequate therapy improve outcomes and reduce the risk of severe visual impairment.

Conclusion

Based on the findings of this study, it can be concluded that both anti-VEGF agents demonstrated clinical efficacy in the management of A-ROP. However, bevacizumab was associated with a significantly lower requirement for supplemental laser photocoagulation and a reduced rate of re-treatment, suggesting a more stable and sustained therapeutic effect compared to ranibizumab. Ultimately, timely screening, accurate diagnosis, and adequate therapeutic intervention facilitate a complete structural and functional resolution of the disease.

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Ethical approval. The Ethics Committee of the Clinical Center of Montenegro, Institute for Children's Diseases, Podgorica, Montenegro, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Neonatalni faktori rizika za razvoj teške forme prematurne retinopatije (A-ROP) i ishod liječenja anti-VEGF terapijom

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Uvod. Retinopatija prematuriteta (ROP) je neurovaskularna bolest koja ukoliko se ne liječi dovodi do teškog oštećenja vida i sljepila. Rana dijagnoza i pravoremena terapija smanjuju rizik za teški ishod. Najznačajniji faktori rizika za razvoj bolesti su niska gestaciona starost, niska porođajna tjelesna masa, razvoj respiratornog distresa i dugotrajna potreba za oksigenoterapijom, neonatalna sepsa, anemija i dr. U ovom radu analizirani su najznačajniji faktori rizika i ishod liječenja anti-VEGF terapijom, te dodatna potreba sa laserfotokoagulacijom.

Metode. Sprovedena je retrospektivna studija u kojoj je učestvovalo 30 djece (60 očiju) sa A-ROP formom retinopatije koja su podijeljena u dvije grupe u odnosu na anti-VEGF preparat koji je primijenjen (bevacizumab ili ranibizumab).

Rezultati. Kada je u pitanju gestaciona starost postoji statistički značajna razlika između dvije grupe. Porođajna tjelesna masa je veća u grupi koja je dobila intravitrealno bevacizumab (IVB). Reaplikacija lijeka je bila potrebna kod 3 pacijenata (5 očiju) liječenih bevacizumabom, te kod 4 pacijenata (9 očiju) koji su dobili ranibizumab (IVR). Potreba za laserfotokoagulacijom je bila 40% u grupi IVB, odnosno 100% u IVR što je statistički veoma značajna razlika.

Zaključak. Pravovremena dijagnoza i adekvatna terapija značajno poboljšavaju ishod i smanjuju rizik od teškog oštećenja vida. U ovom istraživanju je bevacizumab pokazao superiornost u odnosu na ranibizumab kada je u pitanju uticaj na reaktivaciju ROP i potrebu za dodatnom laserskom intervencijom.

Ključne riječi: ROP, retinopatija prematuriteta, anti-VEGF, bevacizumab, ranibizumab