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Case Series

One year follow-up of intravitreal bevacizumab injection in Aggressive Retinopathy of Prematurity at Indonesian national referral hospital: Case series

Dian Estu Yulia*, Diajeng Ayesha Soeharto

Department of Ophthalmology, Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo National Hospital, Jakarta, Indonesia

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ABSTRACT

Purpose: To report the outcomes of children treated with intravitreal Bevacizumab (IVB) for Aggressive Retinopathy of Prematurity (A-ROP) at an Indonesian national referral hospital.

Methods: This retrospective case series was conducted on all A-ROP patients who underwent IVB injection at a referral hospital in Indonesia in 2017–2020. Primary outcomes included regression, subsequent procedure, refractive error, and side effects.

Results: Four patients (seven eyes) were included, with mean gestational age 29.8 weeks. Mean postmenstrual age at injection was 35 weeks. Mean duration from IVB injection to laser photocoagulation was nine days. ROP had regressed in all patients at one-year follow up after injection, and patients presented no systemic side effects.

Conclusion: Use of IVB injection in A-ROP patients could be beneficial to prevent disease progression, and concomitant laser treatment can lead to better outcome. Prospective, larger sample size studies with long-term follow-up is needed.

1. Introduction

Retinopathy of prematurity (ROP) is one of the leading causes of neonatal blindness in the world, and is of particular concern in developing countries such as Indonesia. One of the rare and severe types of ROP is Aggressive Retinopathy of Prematurity (A-ROP). It is defined as a severe progressive form of ROP that is characterized by its rapid development of pathologic neovascularization and severe plus disease that does not follow the typical progressions through ROP stages. Due to its rapid nature, it is considered severe and may potentially lead to blindness [1–3].

Recently, anti-VEGF agents have been used for the treatment of A-ROP, this includes intravitreal Bevacizumab (IVB) and Ranibizumab, with IVB being more commonly used due its wider availability worldwide. Although Ranibizumab is more promising due to its shorter half-life, one study reported that reactivation was more frequently observed in Ranibizumab compared to Bevacizumab [4]. Injection of Bevacizumab in A-ROP should be done within 24–72 h to maximize the outcome [5].

Anti-VEGF could be used as monotherapy in A-ROP patients, although other studies have also highlighted favourable outcomes in combined therapy of IVB and laser photocoagulation [6,7]. The aim of this study was to demonstrate the outcome of IVB in A-ROP patients at our Indonesian hospital.

2. Methods

This retrospective, single-centre, consecutive case series was conducted at an Indonesian academic hospital, Cipto Mangunkusumo National Central Public Hospital. All medical records from A-ROP patients who underwent IVB injection procedure between the years 2017–2020 were collected retrospectively. Diagnosis of A-ROP was made based on International Classification of ROP (ICROP) [2]. All subjects who met the inclusion criteria were included in this study, which were as follows: all patients with A-ROP that received IVB injection procedure between the years 2017–2020 were collected retrospectively. Diagnosis of A-ROP was made based on International Classification of ROP (ICROP) [2]. All subjects who met the inclusion criteria were included in this study, which were as follows: all patients with A-ROP that received IVB injection procedure, with one-year follow-up data after surgery. Medical records that had incomplete data or patients who were lost to follow-up were excluded from this study.

Intervention was given as follows: prior to the procedure, informed consent was obtained, and patients were ensured to be

* Corresponding author. Department of Ophthalmology, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo National Hospital, Jl. Kimia, No. 8, Jakarta, Indonesia.
E-mail address: dian.estu@ui.ac.id (D.E. Yulia).
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hemodynamically stable. Patients were given mydriatic eyedrops before the procedure. The patients were given 0.025 mL (0.25 mg) of IVB injection to their damaged eyes in the operating theatre by the same consultant pediatric ophthalmologist (DEY) using standardized procedure. The patients were then evaluated for outcome in terms of refractive error and complications at one year follow-up. This case series was reported in line with the PROCESS 2020 guidelines [8].

3. Results

Seven patients were included at the initial phase of the study; however, three patients were excluded due to loss to follow-up. Thus, a total of four patients (seven eyes) were included in this case series. Demographic data of patients are shown in Table 1. The mean gestational age was 29.8 weeks, and mean birth weight was 1398 g. Mean Post Menstrual Age (PMA) at the time of injection was 35 weeks. All patients in this study required further laser photocoagulation therapy following IVB, with mean duration of nine days from IVB to laser therapy. ROP had regressed in all four patients during the one-year follow up period after IVB injection. These children could see well, however, most had myopia as a sequela of ROP. All patients had no systemic side effects following the injection. Funduscopic images of one of the patients prior to different stages of treatment is shown in Fig. 1.

Table 1
Patient demographic data, risk factors, and side effects.

| Patient | Sex | GA (weeks) | BW (g) | PMA at first exam (weeks) | Eye | Refractive Error | Risk Factors | Duration from IVB injection to laser (days) |
|---------|-----|------------|--------|--------------------------|-----|------------------|-------------|------------------------------------------|
| 1       | Female  | 33         | 1300   | 37                       | OD  | OD: S −7.00, OS: S −6.00 | Oxygen      | 7                                        |
| 2       | Male   | 30         | 1600   | 34                       | ODS | ODS: S: −2.25 C:1.00 x 180, OS:S:2.00 C:0.50x180 | Oxygen      | 7                                        |
| 3       | Male   | 33         | 2300   | 34                       | ODS | ODS: S: −2.00 C:1.00 x 180, OS:S:2.50 C:0.50x180 | Oxygen      | 14                                       |
| 4       | Male   | 32         | 1600   | 34                       | ODS | ODS: S: −3.00 C:1.00 x 90, OS:S:3.00 C:0.50x90 | Oxygen, Sepsis, Transfusion | 7                                        |

GA: Gestational age; BW: Birth weight; PMA: Post-menstrual age OD: Ocula dextra; OS: Ocula sinistra; ODS: Ocula dextra & sinistra; IVB: Intravitreal Bevacizumab.

4. Discussion

The use of IVB injection in A-ROP patients at our hospital in Indonesia showed good outcomes in terms of regression of disease. This is supported by studies by Law et al. which described that IVB injection might be beneficial for regression of A-ROP [9]. It is worth noting that several days following IVB, it was determined that the peripheral retina of all included patients needed laser treatment. All our patients received laser treatment following IVB injection showed good progression and regressed completely at follow-up, implying that combination therapy potentially had better outcome. Similarly, a study by Hu et al. described all eyes treated with initial monotherapy IVB required re-treatment with either laser photocoagulation, surgery, or a second IVB injection. Re-treatment was required due to progression or recurrence of ROP, in which the latter was defined as by extraretinal fibrovascular proliferation, anterior progression of retinal vasculature, and plus disease. They noted that laser was potentially the preferred method of re-treatment as these eyes had successful outcome and did not require further treatment, whereas eyes that received a second IVB injection required further laser therapy, and some eyes developed retinal detachment. Recurrence or progression following monotherapy IVB was observed at a significant rate in previous studies, and typically at later intervals in comparison to primary laser treatment, and this may be due to the transient action of IVB in its inhibition of VEGF in contrast to long-term downregulation of laser photocoagulation [7,10]. Other studies on combined therapy of IVB and laser photocoagulation with good outcomes support the notion...
that combined therapy is potentially preferable [11,12]. In this study, all patients could see well and had no systemic adverse events from IVB injection at last follow-up. This is supported by a study done by Law et al. [9] which also described no obvious systemic toxicity in their cohort.

Myopia is known to be associated with laser therapy in ROP; and all patients in this study developed myopia after treatment. Harder et al. found that a single intravitreal bevacizumab injection compared to conventional retinal laser coagulation led to less myopization and less astigmatism [13]. It is also supported by a study conducted in Japan that preterm infants who have received multiple laser photocoagulation therapy may be at risk of developing myopia at one-year corrected age [14].

This study is the first to report results of IVB use in A-ROP children in Indonesia. Although the technique may not be novel worldwide, relatively limited availability of the drug in developing countries such as Indonesia thus makes this technique quite novel in our country. This study hence highlights the promising role of IVB as a minimally invasive procedure that can effectively prevent disease progression in A-ROP patients. Limitations of this study include the small sample size and limited follow-up of one year. Further prospective, larger, long-term studies in our population is recommended.

5. Conclusion

In conclusion, use of IVB injection at the most appropriate time frame in A-ROP patients could be beneficial to prevent disease progression. Notably, patients in our study still needed laser therapy. A prospective, larger population, and long-term follow up should be conducted.

Ethical approval

This study was in accordance with the tenants of the Declaration of Helsinki. Ethical approval was not required for case reports at our institution.

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The authors declare no sources of funding.

Author contribution

Dian Estu Yulia: study concept, study design, data collection, data analysis, writing the paper, final approval. Diajeng Ayesha Soeharto: data collection, data analysis, writing the paper, final approval.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

1. Name of the registry:
2. Unique Identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

The Guarantor of this study is Dian Estu Yulia.

Provenance and peer review

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Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104853.

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