Original Article

Treatment of Retinopathy of Prematurity by Intravitreal Injection of Bevacizumab

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Abstract

Introduction: Retinopathy of prematurity is a vasoproliferative disease of the developing retina that is a significant cause of paediatric morbidity and blindness worldwide. Although management by early treatment ROP (ETROP) criteria has led the way to improving the outcomes of treatment-requiring posterior (zone 1) ROP, the failure rate continues to be significant for aggressive disease. Managing a premature infant with ROP is a significant challenge to ophthalmologists and associated physicians. However, increasingly younger and lower birth-weight infants can survive with advances in neonatal care.

Objectives: To assess the effectiveness of intravitreal injection of Bevacizumab on regression of retinal neovascularization in stage III, Zone 1, 2 retinopathy of prematurity and aggressive posterior retinopathy of prematurity.

Methods: Intravitreal Injection of Bevacizumab (0.625mg/0.025mL) was performed on 34 eyes of 17 newborns with stage III, Zone 1, 2 retinopathy of prematurity and aggressive posterior retinopathy of prematurity. The changes in retinal neovascularization were assessed by frequent fundoscopy.

Results: Retinopathy of prematurity regressed in all the eyes treated. The retinal vascularization proceeded beyond the demarcation line. Four eyes of 2 patients needed repeat injections. One eye needed an additional laser. There was no injection-related complication observed.

Conclusion: Intravitreal injection of Bevacizumab can be considered an effective modality in treating Retinopathy of Prematurity. It is recommended to perform more studies to assess its long-term effect on the body's vascular system.

Key words: Retinopathy of prematurity, Intravitreal injection, Bevacizumab.

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retina which causes significant paediatric morbidity and blindness throughout the world[1,2]. Infants with ROP presents a significant challenge to all physicians treating premature infants. However, increasingly younger and lower birth-weight infants can survive with advances in neonatal care. Although management by early treatment ROP (ETROP) criteria has improved the outcomes for treatment-requiring posterior (zone 1) ROP[3], the failure rate continues to be significant for aggressive conditions. The disease can progress despite treatment. The application of conventional laser for treatment-requiring ROP in zone 1 or posterior zone 2 involves the destruction of a large area of the avascular retina with a potentially higher risk of complications and morbidity for the child.

Managing the aggressive posterior-ROP (AP-ROP) is a real challenge and difficult. AP-ROP may develop very fast to retinal detachment if not managed early. In a case series, reported the outcomes with zone 1 ROP. Among them, 17 of 48 eyes with anterior zone 1 ROP and 9 of 9 eyes with posterior (zone 1) ROP had unfavourable effects following laser photocoagulation therapy. It is still not uncommon for AP-ROP to progress despite timely and appropriate treatment with laser[4,5]. Pharmacotherapy for ROP may help to improve the effects in some of these problematic cases. Over the past five years, intravitreal Bevacizumab (Avastin, Genentech) has become more popular for the management of retinopathy of prematurity.

Vascular endothelial growth factor (VEGF) is critical in normal vascular development and ROP's pathogenesis. Studies have reported that physiologic levels of VEGF are necessary to maintain and stimulate normal vascular growth[6]. A very premature baby is placed in a hyperoxic environment and VEGF production is down regulated which prevents immature vessels to stop growing. This produces peripheral avascular retina in the

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premature infant. The more immature the infant, the larger the avascular area is likely to be. Ultimately, the avascular retina becomes ischemic and helps in stimulating VEGF production. The high aggregation of VEGF can help to develop ROP and neovascularization. These can cause vasodilatation and tortuosity of vessels, ultimately developing the plus disease. Rubeosis iridis may also ensue[6]. The management of the peripheral avascular retina with cryotherapy or laser therapy promotes a reduction of VEGF levels which then induces regression of neovascularization[7]. To evaluate the effects of intravitreal injection of Bevacizumab on regression of retinal neovascularization in stage III, Zone 1, 2 retinopathy of prematurity and aggressive posterior retinopathy of prematurity.

Materials and Methods

This prospective study was done in the eye department and paediatric department of Combined Military Hospital, Dhaka. Zone 1 was defined according to the international classification of retinopathy of prematurity revisited[7] as a circle whose radius is two times the distance between the centre of the optic disc and the centre of the macula. Posterior zone 2 was defined as a circle whose radius extends from the centre of the optic disc to the nasal ora serrata.

Only patients with bilateral moderate or severe stage 3 ROP were considered candidates for this study. No infant with a congenital systemic or ocular anomaly was included in this series. Two infants were referred with preexisting severe stage 3 ROP and treated immediately. One infant presented with AP-ROP. The screening was done by current criteria and treated immediately[8]. However, when mild stage 3 ROP was identified in eight infants with debatable plus disease, they were observed until the development of moderate stage 3 ROP with definite plus disease. This approach intended to minimize the number of treated cases that might have spontaneously regressed.

The timing of the injections was later than recommended by the early treatment of retinopathy of prematurity study[3] but earlier than the cryotherapy for retinopathy of prematurity study[9] with definite plus disease. No infant was treated before definite plus disease was present. All infants were followed closely by indirect ophthalmoscopy for recurrence; however, no recurrences developed. The injections were done under intravenous injection of Midazolam 50 to 150 microgram/kg/dose 10 to 15 minutes before the procedure in operation theater. Intravitreal injection of Bevacizumab (0.625mg/0.025mL) was performed on 34 eyes of 17 newborns with stage III, Zone 1, 2 retinopathy of prematurity and AP-ROP. Sterile gloves, wire speculum and forceps were utilized while administering the injections. A speculum for premature infants was placed between the lids. A drop of povidone-iodine (5%) ophthalmic solution was placed into the conjunctival sac for 1 minute with the excess removed by a sterile cotton tip applicator from the temporal lid margin. The eye was stabilized with toothed forceps while the dose of Bevacizumab (0.025mL [0.625mg]) was injected behind the lens. The needle, aimed posteriorly (toward the optic nerve), entered the sclera through the conjunctiva 1.5mm behind the limbus and was advanced approximately two-thirds of the length of the needle (not to the hub). The syringe was entirely emptied into the central vitreous. (Whether the injection was through the undeveloped pars plana or the most anterior, avascular, undifferentiated peripheral retina, care was taken to avoid the vast lens of the premature infant.) After the injection, povidone-iodine was again placed into the conjunctival sac for 1 minute with the excess removed by a sterile cotton tip applicator from the temporal lid margin. The speculum was then removed from between the lids. The same procedure was performed for the other eye.

An ophthalmic antibiotic drop, Tobramycin 0.4% solution was prescribed for both eyes to begin immediately and be continued every 6 hours for seven days after the bilateral intravitreal injections. Indirect ophthalmoscopy was utilized to look for any injury to the lens to determine the presence of adequate blood flow through the central retinal artery and to identify any retinal tears or vitreous haemorrhage immediately after the injection. With the lid closed, tactile pressure was determined. Indirect ophthalmoscopy was also performed the following day to look for any sign of vitreous infection specifically. None of those mentioned above complications was encountered. The changes in retinal neovascularization were assessed by frequent fundoscopy.

Results

This study was a prospective, consecutive, non-comparative case series of 34 eyes of 17 patients. Four of the infants had confirmed sepsis. The mean birth weight for the seven infants with ROP in posterior zone 2 was 790gm (mean gestational age, 24.9 weeks) compared with 570gm (mean gestational age, 23.3 weeks) for the four infants with ROP in zone 1. The five infants with ROP in posterior zone 2 generally had fewer and less severe systemic complications. The Retinopathy of prematurity regressed in all the eyes treated. The retinal vascularization proceeded beyond the demarcation line. Four eyes of 2 patients needed repeat injections. One eye needed an additional laser. There was no injection-related complication observed. No trauma to the ocular structures was identified and no endophthalmitis occurred.

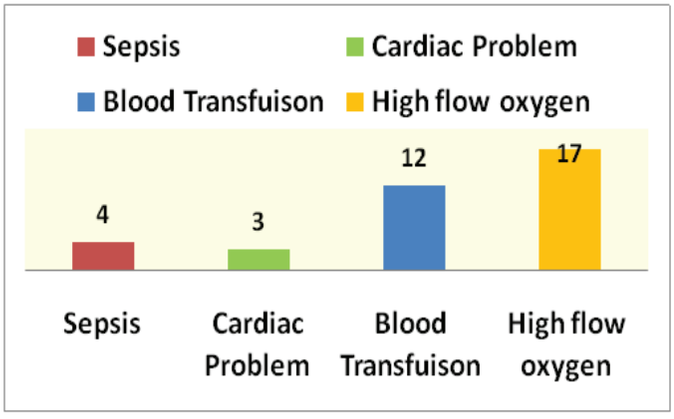

Figure-1: Co-morbidities of premature infants

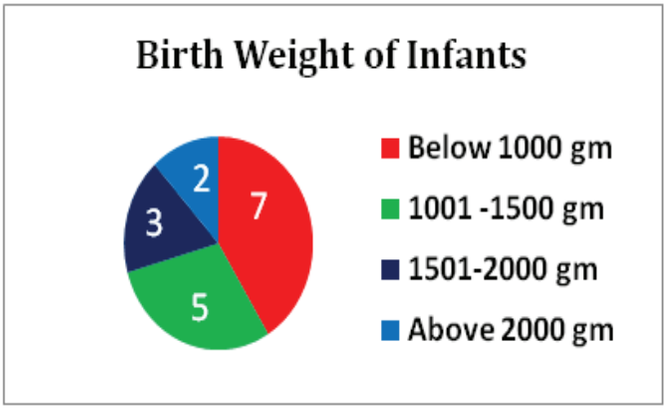

Figure-2: Birth weight distribution of the premature babies

Discussion

ROP is a VEGF-driven disease and reducing VEGF levels promotes neovascularisation regression; intravitreal anti-VEGF agents have been utilized to treat this condition. Quiroz-Mercado et al[8,9] reported results in 18 eyes with ROP treated with Bevacizumab for both primary and salvage therapy. All patients required one or more injections of Bevacizumab to promote regression of disease[8]. Neovascularization regressed in all cases; to date, no serious adverse events have been seen in this series with five years of follow-up.

A study was initiated to investigate the safety and efficacy of intravitreal Bevacizumab on ROP, BEAT ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity)[10] and BLOCKROP (Pan-VEGF Blockade for the Treatment of Retinopathy of Prematurity)[11]. In February 2011, Mintz-Hittner et al[12] presented the BEAT-ROP results, demonstrating a better intravitreal Bevacizumab result than conventional laser therapy for ROP in stage 3 with the plus disease of Zone 1. Although the results of the BEAT ROP study are vitalizing, the long-term complications of intravitreal Bevacizumab therapy for ROP have not been fully illustrated. Few local adverse effects, such as vitreous haemorrhage and progression to retinal detachment after anti-VEGF therapy, are reported in the literature[13,14].

Infection, rhegmatogenous retinal detachment and cataracts are potential complications after the injection. However, the primary concern of anti-VEGF treatment for ROP is essential for preventing normal vascular development. Delayed normal vascularization is a concern, as areas of peripheral retinal nonperfusion may develop after intravitreal bevacizumab[15].

Intraocular injection of Bevacizumab has a rapid and profound effect on flat neovascularization and disease, including venous dilation, arteriolar tortuosity, vitreous haze, iris vascular engorgement and pupillary rigidity. All these undergo marked diminution within 24 hours and virtually complete resolution within 48 hours. Elevated neovascularization, termed "extraretinal fibrovascular proliferation," also involutes but at a much slower rate which may be a function of larger tissue volume. This neovascularization becomes grey within one week, turns white, becomes less dense and eventually separates from the retina. Months later, the extraretinal fibrovascular proliferation is often difficult to locate but may be seen as a white wisp or linear remnant floating in the vitreous[16]. The results of BEAT ROP demonstrated that "intravitreal bevacizumab should become the treatment of choice for zone 1 retinopathy of prematurity[10]." It is clearly estimated that intravitreal Bevacizumab is an effective treatment modality in promoting regression of treatment-requiring ROP.

Therefore, whether the neovascularization is flat or elevated in zone 1 or posterior zone 2, the response to anti-VEGF therapy is the regression of abnormal vessels and the advancement of normal retinal vessels. However, the growth of normal retinal vessels after intravitreal injection of Bevacizumab is often slower than that of normal retinal vessels. Thus, vascularization does not necessarily always extend to the ora Serrata if the infant is significantly premature and vascularization may be slower than usual, so the time to discontinue retinal examinations is less certain[17]. These preliminary results are promising without any early local or systemic complications. The consistent success of intravitreal injections of Bevacizumab in this minimal series of 34 eyes with moderate and severe stage 3 ROP (retinopathy of prematurity) in zone 1 or posterior zone 2 warrants a prospective, randomized, controlled, multicenter clinical trial.

Conclusion

Intravitreal injection of Bevacizumab can be considered an effective modality in treating Retinopathy of Prematurity. Intravitreal anti-VEGF therapy for ROP has a significant global impact. It is recommended to perform more studies to assess its long-term effect on the body's vascular system.

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