Intravitreal Avastinin Management of Retinopathy of Prematurity

Khaled AG Shalaby[1, 2] and Ashraf Alawadi Abdullhameed[3, 4]

[1]Opthamology Department, Al-Azhar University, Cairo, Egypt
[2]Chief Vitreoretinal Service, Dr Soliman Fakeeh Hospital, Jeddah, Saudi Arabia
[3] Pediatric Department, Al-Azhar University, Cairo, Egypt;
[4]Chief of neonatal intensive care unit, United Doctors Hospital (UDH), Jeddah, Saudi Arabia
kagretina@gmail.com, ashalawadi5@hotmail.com

Abstract: Purpose: To evaluate the therapeutic effect of intravitreal bevacizumab in management of eyes with threshold retinopathy of prematurity (ROP) and its impact on avoiding the conventional destructive peripheral retinal laser ablation.**Methods:** Thirty one consecutive infants (62 eyes) who suffered threshold retinopathy of prematurity and received one or repeated intravitreal bevacizumab (IVB) (0.625 mg in 0.025 ml of solution) were enrolled in this non-comparative retrospective study. They were intravitreally injected between August 2009 and December 2011 in one center (Dr Soliman Fakeeh Hospital, Jeddah, Saudi Arabia). The primary ocular outcome was recurrence of retinopathy of prematurity requiring conventional laser retreatment. **Results:** Thirty one infants (62 eyes) were recruited to retrospective non-comparative study. The mean gestational age was 27.2±1.2 weeks (mean ± standard deviation); (range: 24–32.2 weeks), mean age at the time of intervention was 37.5±2.4 gestational weeks (range: 32.4–43.2 weeks), and mean follow-up was 32.4±21.9 weeks. The mean birth weight was 810±205 g (range: 650–1500 g). All eyes showed a regression of the retinal neovascularization and plus disease within 2–7 days, with a decrease in pupillary rigidity within 2–4 weeks. In 4 (13.3%) infants (8 eyes), a second intravitreal bevacizumab was performed. Ten (32.2%) infants (20 eyes) needed peripheral retinal laser ablation 4-8 weeks after injections and 4 infants of them received tow injections of IVB before laser treatment. One (1.6%) infant with cardiopulmonary congenital abnormalities died during the follow up period after 2 months of IVB with complete regression of retinal neovascularization. One (1.6%) eye developed peripheral lens injury and 9 (15%) eyes showed subconjunctival hemorrhages after IVB. **Conclusions:** Intravitreal bevacizumab in infants with threshold retinopathy of prematurity is generally safe and effective and can replace the conventional laser treatment. This study was too small to assess safety and appropriate long term post injection monitoring is recommended.
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1. Introduction

Retinopathy of prematurity (ROP), previously called retrolental fibroplasia, Terry's syndrome is a proliferative retinal disorder considered as a leading cause of childhood blindness worldwide. It is mainly associated with early gestational age and low birth weight (≤1,250 g). ROP causes visual loss by means of macular dragging, vitreous hemorrhage, and retinal detachment.[1, 2] The first case of ROP was described by Theodore L. Terry in 1942. He described the Affected eyes being exhibited a grayish-white, opaque membrane behind the crystalline lens. He suggested that it might have resulted from "fibroblastic overgrowth of a persistent tunica vasculosa lentis. [2] In 1951, Campbell first suggested the relationship between the ROP and introduction of oxygen therapy into the newborn nursery.[3] During the 1940s and 1950s, ROP, was the leading cause of blindness in children in the United States.[4] ROP is a biphasic disease characterized by oxygen-induced attenuation of normal retinal vascularization followed by hypoxia-induced vasoproliferation.[5] Both phases are mediated by growth factors, including the proangiogenic cytokine vascular endothelial growth factor. A growing body of laboratory and clinical evidence supports the rationale of targeted pharmacologic inhibition of VEGF as a treatment for acute phase ROP.[6, 7]

Although our understanding of oxygen management has significantly improved in the last half-century, the number of infants with ROP has risen, likely due to increased survival of very low birth weight and younger infants. Fortunately, due to good neonatal care and appropriate screening and treatment, the incidence of blindness due to ROP is only one case in 820 infants.[8] Complications of ROP include myopia, early development of cataracts, iris neovascularization, glaucoma, retinal pigmentation, retinal folds, dragging of the retina, lattice-like degeneration, retinal tears, and rhegmatogenous and exudative retinal detachments. [1, 9-13]

The International Classification of Retinopathy of Prematurity, published in 1984, defined ROP in terms of location (zones I-III), severity (stages 1-5), extent (clock hours 1-12), and vascular dilatation and

tortuosity (Plus disease). It is important to note that stages are based on the vessel appearance at the interface between the vascular and avascular retinal areas, and staging is crucial in deciding the timing of treatment. In stage 1, the interface is a line, while it resembles a ridge in stage 2. New vessels grow onto the ridge and extend into the vitreous cavity in stage 3 and continue as fibrous bands leading to partial retinal detachment in stage 4. Finally, total retinal detachment can ensue in stage 5. [14, 15]

Both CRYO-ROP [16] and Early Treatment ROP [17] demonstrated improvements in the structural and functional outcomes with peripheral ablation therapy. The role of VEGF in the pathogenesis of ROP has been described. [18]Anti-VEGF has been administered off-label successfully in many VEGF mediated diseases such as neovascular AMD, retinal vein occlusion[19], proliferative diabetic retinopathy [20, 21], diabetic macular edema [22] anterior segment neovascularization with PDR [23, 24], CNV caused by pathological myopia[25] , idiopathic CNV [26], pseudophakic cystoid macular oedema[27]and retinopathy of prematurity. [28]The number of patients who have undergone this therapy for ocular disease has increased markedly in the last few years.

Many recent reports of anti-VEGF use in ROP showed that it can be a safe and effective treatment [15, 18, 29, 30]. However, there is concern about the choice of the drug, dose and time of injection as well as about local and systemic potential complications [8, 18].

The current doses of intravitreal bevacizumab varies from 0.625 mg to 0.75 mg and it has not shown systemic or local toxicity. The most likely local complications of the injections are infectious and traumatic to the lens. No systemic complications have been encountered to date. [31, 32]

The purpose of the study is to evaluate the therapeutic effect of intravitreal bevacizumab in management of eyes with threshold retinopathy of prematurity (ROP) and its impact on avoiding the conventional destructive peripheral retinal laser ablation.

2. Methods

Thirty one consecutive infants (62 eyes) who suffered threshold retinopathy of prematurity and received one or repeated intravitreal bevacizumab (IVB) (0.625 mg / 0.025 ml) were enrolled in this non-comparative retrospective study. They were intravitreally injected between August 2009 and December 2011 in one center (Dr Soliman Fakeeh Hospital, Jeddah, Saudi Arabia). The primary ocular outcome was recurrence of retinopathy of prematurity requiring conventional laser retreatment.

Exclusion criteria included history of primary laser treatment, ROP with retinal detachment, ocular inflammatory disease, refusal of informed consent from a parent or guardian and infant who had been followed-up for a period of less than six months. The ‘‘off-label’’ status of this medication, and possible systemic and ocular complications, were discussed in detail and informed consent was obtained from all parent or guardian. Institutional review board/ethics committee approval was obtained for this study. All eyes underwent full pre-injection and post-injection assessment included general examination by neonatologist and dilated fundus examination using indirect ophthalmoscopy and +28 lens and B-scan ultrasonography in eyes with opaque media. The ROP stage and plus disease were defined on the basis of the revised international classification of ROP.[14]Each patient received one or repeated IVB which was prepared by the hospital pharmacy as 0.065mg /0.025 ml injections in an insulin syringe for each patient from commercially available 4 ml vial of bevacizumab (25mg/ml) under aseptic techniques. After the application of topical anesthesia using proparacaine hydrochloride 1% ophthalmic drops, the eye and lids were disinfected with 10% povidone iodine. 0.065 mg/0.025ml of bevacizumab was injected intravitreally through the pars plicata 1-1.5 mm posterior to the corneal limbus into the vitreous cavity using a 27 or 30 gauge needle. The injection site was compressed for several seconds to avoid reflux when the needle was removed. The IOP was assessed and the nurses were instructed to use topical gatifloxacin eye drops 0.3% Q6H for 5 days. All enrolled eyes in this study were injected inside the neonates intensive care unit (NICU) by one vitreoretinal surgeon. All infants were examined (generally and ophthalmologically) within 1 week, at 1 month and at 2 or 3 months after the injection. During the follow-up period, fundus examination was performed with special emphasis on ocular or general complications. Statistical analysis where appropriate, the Chi-square test, Fisher exact test, and analysis of variance tests were used to get correlations between baseline ocular characteristics and the anatomical and functional outcomes. Statistical analyses were performed using STATA for Windows version 8.0 (StataCorp Inc, College Station, Texas, USA).

3. Results

The patient characteristics are shown in table 1. Thirty one infants (62 eyes) were recruited to retrospective non-comparative study. The mean gestational age was 27.2±1.2 weeks (mean ± standard deviation); (range: 24–32.2 weeks), mean age at the time of intervention was 37.5±2.4 gestational weeks (range: 32.4–43.2 weeks), and mean follow-up was 32.4±21.9 weeks. The mean birth weight was 810±205 g (range: 650–1500 g). Twenty patients were

on oxygen therapy and 6 of them requiring ventilator. Out of the 62 eyes, 50 (80.6%) eyes had stage 3+ ROP, 10 (16.1 %) had stage 4a+ and 2 (3.2 %) eyes had stage 4 with dense vitreous hemorrhage. The most common zone involved was zone 2 (45, 72.6 % eyes) followed by zone 3 (10, 16.1 % eyes) and then zone 1 which was involved in 7(11.3 %) eyes (table 1). All eyes showed a regression of ROP in the form of decreased retinal neovascularization and plus disease (decreases in venous dilatation, arterial tortuosity) within 2–7 days, with a decrease in pupillary rigidity within 2–4 weeks. In eyes that had extraretinal fibrovascular proliferation, this became involuted and appeared as a disconnected, whitish islands of fibrous tissues. There was complete disappearance of rubeosis in all eyes. In 4 (13.3%) infants (8 eyes), a second intravitreal bevacizumab was performed with 5-8 weeks interval. Ten (32.2%) infants (20 eyes) needed peripheral retinal laser ablation 4-8 weeks after injections and 4 infants of them received tow injections of IVB before laser treatment. One (1.6%) eye with dense vitreous hemorrhage underwent vitrectomy because of persistent central intragel vitreous hemorrhage associated with vitreo-papillo-macular traction membranes. This eye was injected twice and received peripheral retinal laser ablation after clearance of peripheral vitreous hemorrhage. One (1.6%) infant with cardiopulmonary congenital abnormalities died during the follow up period after 2 months of IVB with complete regression of retinal neovascularization. One (1.6%) eye developed peripheral lens injury and 9 (15%) eyes showed subconjunctival hemorrhages after IVB. No systemic side effects of bevacizumab were observed.

Table 1 Baseline patients and ocular characteristics (n = 31 infants, 62 eyes)

Mean gestational age *(weeks) (range)*	**27.2±1.2 (24–32.2)**
Mean age at the time of injection(weeks),± *SD (range)*	37.5±2.4 (32.4–43.2)
Mean birth weight(gram)	810±205 (650–1500)
Mean follow-up(weeks)	32.4±21.9
Sex:	
Male	14 (45.2%)
Female	17 (54.8%)
ROP, stage	
Stage 3+	50 (80.6%)
Stage 4a+	10 (16.1%)
Stage 4 (vitreous hemorrhage)	2 (3.2%)
ROP, Zone	
Zone ***I***	7 (11.3%)
Zone ***II***	45 (72.6%)
Zone ***III***	10 (16.1%)

Abbreviation: SD, standard deviation.

Table 2 Outcomes and complications (n =31 infants, 62 eyes)

Regression of RN	**62 (100%)**
Repeated intravitreal bevacizumab	8 (13.3%)
Peripheral retinal laser	20 (32.2%)
Vitrectomy	1 (1.6%)
Died number (%)	1 (1.6%)
Postoinjection complications	
Lens injury	1 (1.6)
Subconjunctival hemorrhages	9 (15)

Abbreviation: RN retinal neovascularization

4-Discussion

While distractive peripheral retinal laser ablation remains the standard of care in the treatment of advanced ROP, regression is not seen in all cases (especially in aggressive posterior ROP, AP-ROP) following laser alone. There are multiple reports using anti-VEGF for ROP treatment. In recent reports, anti-VEGF was used as first-line therapy with complete regression of neovascularization without the need for further treatment. [29]

Mintz-Hittner and Kuffel [18] reported that intravitreal injection is a safe and effective treatment for stage 3 ROP in zone I and II. No systemic complications have been reported to date. Some authors consider that long-term systemic complications are unlikely following a single injection of a small

quantity of anti-VEGF into the vitreous cavity. [15] Some authors preferred to use ranibizumab because it has a shorter systemic half-life than bevacizumab, in attempt to reduce the risk of systemic complications in premature infants. Several investigators have confirmed the reductions in the systemic VEGF levels 1–2 weeks following IVB, which seems to continue for several days. [33, 34]

Potential benefits of using anti-VEGF treatment include eliminating visual field loss due to retinal laser ablation. Injections may be administered in very sick infants to avoid general anesthesia risks, and they are easy to perform even in infants with opaque media because of anterior segment involvement. [18] The vascularization of the preterm peripheral retina is a finite process and once the peripheral inner retinal vessels develop, the disease process does not recur. [18]Low et al [31] highlighted that treatment with bevacizumab may be used to improve visualization for more definitive laser or surgical treatment and may facilitate disease regression without obvious systemic toxicity. Azad et al.[35]stressed that anti-VEGF agent in ROP, both as monotherapy and as rescue therapy, need thorough investigation, using well-designed scientific protocols, with informed consent, and monitoring of the long-term ocular, systemic, and developmental outcomes.

The current study reported 67.8% (42 out of 62 eyes) success rate of using IVB as monotheraby for threshold ROP. The remaining 20 (32.2%) eyes needed augmentation of the IVB by the standered peripheral laser photocoagulation. The time interval between the IVB and the initiation of laser treatment (5-8 weeks) gave the very sick preterm the chance to gain more weight and to improve his general condition to be fit for general anesthesia. Micieli et al. [30] showed some variability in the off-label use of bevacizumab, mainly regarding dose, time of injection and frequency of administration.

ROP is less likely than choroidal neovascularization or diabetic retinopathy to necessitate repeated injections since the disease is known to undergo spontaneous involution in 90% of patients after 44 weeks of postmenstrual age. [28]In the current study IVB was repeated in only 8 (13.3%) eyes.

Complications can occur with intravitreal injections of anti VEGF. The most likely local complications of the injections are infectious and lens injury. No systemic complications have been encountered to date. [31, 32] Jang et al. [36] reported bilateral retinal detachment 3 months after combined laser and intravitreal ranibizumab despite of full regression. This kind of complication can be considered as a procedure-related rather than a drug-related complication. The current study reported a procedure-related complication in the form of peripheral lens injury in one (1.6 %) eye and subconjunctival hemorrhages in 9 (15 %) eyes. Honda et al.[37] reported drug-related complication in the form of funnel-like retinal detachment after intravitreal bevacizumab for stage 4a ROP due to acute contraction of the proliferative membrane.

Conclusions

This study is limited by its retrospective non-comparative nature and by the relatively short follow up period. Nonetheless, the study highlights the effectiveness of IVB in infants with threshold ROP which can replace the conventional laser treatment. Other limitation of the current study is the lack of preoperative and postoperative photographic documentation due to lack of availability of a digital portable fundus camera. Although the current study showed no signs of significant systemic or ocular adverse side effects until the time of this report, further investigation and appropriate long term post injection monitoring is recommended.

Corresponding author
Khaled AG Shalaby[1, 2]
[1]Opthamology Department, Al-Azhar University, Cairo, Egypt
[2]Chief Vitreoretinal Service, Dr Soliman Fakeeh Hospital, Jeddah, Saudi Arabia
kagretina@gmail.com,
kasoliman@hotmail.com

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