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PARADIGM SHIFT IN MANAGEMENT OF ROP: FROM LASERS TO ANTI-VEGF THERAPY

Ophthalomology

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ABSTRACT

AIM: To investigate the efficacy, safety, and anatomical outcomes associated with intravitreal anti-vascular endothelial growth factor (VEGF) (ranibizumab) in treatment of retinopathy of prematurity (ROP).

METHODS: A retrospective study of 24 infants (48 eyes) was conducted from April 2017 to July 2018. All infants were diagnosed with ROP and primarily treated with intravitreal anti-VEGF Ranibizumab (IVR). The treatment success was defined as complete regression of retinopathy and vascularization into zone 3.

RESULTS: A total of 48 eyes were treated with ranibizumab. Mean birth weight was 1.47±0.32 kg. Gestational age at birth was 32.25±1.32wk, and post-menstrual age at treatment was 36.08±1.61wk. Aggressive posterior ROP was found in 41.7% of subjects. Mean follow-up period was 9.58±1.97 months. Treatment success was observed in 36/48 eyes (75%) with primary intervention only. Remaining six infants [12/48 eyes (25%)] required secondary laser to achieve treatment success. Retreatment occurred at a mean of 7.8 weeks after initial IVR treatment (range 6-10wk).

CONCLUSION: Intravitreal anti-VEGF treatment of ROP with ranibizumab achieved stable retinal vascularization with a low rate of complications and recurrence.

KEYWORDS

retinopathy of prematurity, intravitreal anti-VEGF, ranibizumab

INTRODUCTION

Retinopathy of prematurity (ROP) is a vaso-proliferative retinal vascular disease typically affecting premature infants, and is one of the leading causes of childhood blindness [1, 2]. Initial stage of hypoxia and subsequent hyperoxia induces release of vascular endothelial growth factor (VEGF), causing abnormal blood vessel growth in the retina [3]. ROP causes 3% to 10% of childhood blindness worldwide. [4, 5].

The incidence of ROP in India is around 15.6%–47.3% and 3.5%-13 % of these infants require treatment. [6-9,10-13] Recently, a rise in the number of newborns admitted to Neonatal Intensive Care Units (NICUs) across India has been observed with an increase in the number of preterm babies with ROP. [14]

Most cases of ROP are mild which resolve spontaneously without any treatment. A small proportion can progress to severe ROP, which, if untreated, will result in retinal detachment or scarring and distortion of the retina with irreversible vision loss. [15]

Young et al published the first study that investigated the association between VEGF and ROP in humans. [16] Beginning in 2007, several reports presented promising experience with off label use of bevacizumab (Avastin, Genentech, San Francisco) and ranibizumab (Lucentis®, Novartis Basel, Switzerland) in infants with progressive ROP.[17-22] The key role played by VEGF in inducing retinal neovascularization (NV) prompted researchers to explore the role of anti-VEGF drugs in the management of ROP.

In the landmark Bevacizumab Eliminates the Angiogenic Threat (BEAT)-ROP study in 2011, Anti-VEGFs were used as the primary treatment for zone 1 and posterior zone 2 ROP.[20] This study showed that anti-VEGF injections allow continued vessel growth into the peripheral retina. In contrast, ablation therapy destroyed large areas of the peripheral retina and may affect associated vascular growth. The benefits of intravitreal anti-VEGF therapy includes increased peripheral vascularization with resulting improvement in the visual field, less macular dragging, less pathological myopia, and ease of procedure without need for general anesthesia [23-25]

Previous studies have shown systemic suppression of growth factors and VEGF post intravitreal injection in neonates. This raises major concerns of neurological or developmental delay and organogenesis [26-28]. There is possibility of additional local complications like retinal detachment and endophthalmitis. [29-31]

Bevacizumab has been more widely used than ranibizumab for treating ROP till now [32]. Ranibizumab is a humanized recombinant antibody fragment derived from bevacizumab, with approximately tenfold greater binding affinity [33, 34]. Smaller molecular weight of ranibizumab (48 vs. 149 kDa) hastens its systemic clearance. The intravitreal half life of Ranibizumab is one fourth of that of Bevacizumab. [35] Ranibizumab also has better efficacy and systemic safety profile as compared to Bevacizumab. [36, 37]

In this study, we assessed the efficacy, anatomical outcomes, and complications of anti-VEGF therapy for ROP using Ranibizumab.

MATERIALS AND METHODS

This was a retrospective study conducted in tertiary referral center. Patients diagnosed with ROP who received intravitreal anti-VEGF treatment from April 2017 to July 2018 were included, and their medical records were reviewed. All relevant co-morbid conditions, risk factors, both maternal and neonatal, were noted. All infants with ROP who required treatment were hospitalized in neonatal intensive care units. This study was conducted with the approval of our institutional review board and adhered to the principles of the Declaration of Helsinki. Informed written consent was taken from the legal guardian of all the newborns.

All newborns were screened for ROP if their gestational age at birth (GA) was less than 32 weeks, their birth weight (BW) was less than 1500 g, or if they had an unstable clinical course as determined by the primary neonatologist. All examinations were performed by qualified retina specialist using the 2005 International Classification of Retinopathy of Prematurity [38]. Indications for treatment were infants who met criteria for type 1 ROP as defined in the ETROP (Early Treatment for Retinopathy of Prematurity) study [39].

Under all aseptic precautions, intravitreal anti-VEGF (ranibizumab; 0.2 mg/0.02 mL; Lucentis, Novartis, Basel, Switzerland) [28, 29] was injected into each eye 0.5 to 1 mm posterior to the limbus under topical anesthesia. [40, 41]

Patients were reexamined on the next day and then on alternate days for one week to monitor for signs of any intraocular infection. Weekly follow up was continued until complete regression of the active ROP (regression of plus disease as well as of any proliferation present at time of treatment) was noted. The follow up was continued monthly till 6 months. All subjects were evaluated for recurrences which could require additional treatment like repeat injection, laser, or surgery.

We defined treatment success as complete regression of retinopathy and vascularization into zone 3. The outcome was declared as primary treatment success, if it was achieved with single IVR injection. It was termed as secondary treatment success if additional laser was given.

Major complications were defined as occurrence of corneal opacity, lens opacity, retinal or vitreous hemorrhage, retinal detachment, optic atrophy or patient mortality.

Statistical Analysis

Qualitative data was represented in form of frequency and percentage. Among Qualitative data, Nominal data included parity, Mode of Delivery, Gender of New-born, presence of Respiratory Distress Syndrome, Medical History, presence of Anemia, AP ROP, etc. Quantitative data was represented using Mean±SD and Median & IQR (Interquartile range). Among Qualitative data, Ordinal data included Stage of ROP (Right and Left Eye) as well as Zone of ROP (Right and Left Eye) and was represented in form of frequency and percentage. Quantitative data included Gestational Age, Post Menstrual Age, Birth Weight etc. PSPP version 1.0.1 was used for statistical analysis.

RESULTS

A total of 48 eyes from 24 infants were included. Gender, BW, GA, ROP classification, and other baseline characteristics are shown in Table 1.

Table 1 Baseline demographics of study population

Sr no	GA	PMA	BW in KG	Mode of Delivery	Sex	Medical history	Stage of ROP	Zone of ROP	AP ROP	Response to Rx	Additional RX	F/U
1	34	38	1.8	LSCS	M	RDS	OD-3	OD-2	Y	Secondary	6week	10
							OS-3	OS-2				
2	30	34	1.75	LSCS	M	Nil	OD-3	OD-3	Y	Primary		12
							OS-3	OS-3				
3	34	38	1.8	Vaginal	M	NIL	OD-3	OD-2	N	Primary		10
							OS-3	OS-2				
4	33	37	1.5	LSCS	F	RDS, Anemia	OD-3	OD-2	N	Primary		10
							OS-3	OS-2				
5	33	36	1.1	LSCS	F	Anemia	OD-3	OD-2	N	Primary		12
							OS-3	OS-2				
6	32	36	1.3	LSCS	M	RDS, Septicemia	OD-3	OD-3	Y	Primary		12
							OS-3	OS-3				
7	32	36	1.5	LSCS	M	Nil	OD-3	OD-2	N	Primary		10
							OS-3	OS-2				
8	31	34	1.2	LSCS	F	Nil	OD-3	OD-2	N	Primary		9
							OS-3	OS-2				
9	31	35	1.3	LSCS	F	Nil	OD-3	OD-3	N	Primary		7
							OS-3	OS-3				
10	31	34	1	LSCS	M	Nil	OD-3	OD-1	Y	Secondary	7week	7
							OS-3	OS-1				
11	34	38	1.2	LSCS	F	Nil	OD-3	OD-2	N	Secondary	8week	6
							OS-3	OS-2				
12	32	36	1.4	Vaginal	M	RDS	OD-3	OD-1	Y	Primary		10
							OS-3	OS-1				
13	31	34	1.1	LSCS	F	RDS	OD-3	OD-2	N	Primary		9
							OS-3	OS-2				
14	32	36	1.8	LSCS	M	RDS, Septicemia	OD-3	OD-2	Y	Primary		10
							OS-3	OS-2				
15	33	37	1.3	LSCS	F	Nil	OD-3	OD-3	N	Primary		7
							OS-3	OS-3				
16	34	38	2.0	LSCS	M	Anemia	OD-3	OD-1	Y	Secondary	8week	12
							OS-3	OS-1				
17	31	35	1.7	LSCS	F	Nil	OD-3	OD-2	N	Primary		7
							OS-3	OS-2				
18	32	36	1.8	LSCS	M	Anemia	OD-3	OD-3	N	Primary		10
							OS-3	OS-3				
19	30	33	1.2	LSCS	M	RDS	OD-3	OD-2	Y	Primary		10
							OS-3	OS-2				
20	34	39	1.7	Vaginal	M	Nil	OD-3	OD-2	N	Primary		6
							OS-3	OS-2				
21	33	37	1.9	LSCS	F	Nil	OD-3	OD-3	N	Primary		10
							OS-3	OS-3				
22	32	36	1.2	LSCS	M	Nil	OD-3	OD-2	Y	Primary		10
							OS-3	OS-2				
23	31	35	1.0	LSCS	M	RDS	OD-3	OD-1	Y	Secondary	8week	12
							OS-3	OS-1				
24	34	38	1.8	Vaginal	F	Nil	OD-3	OD-2	N	Secondary	10 week	12
							OS-3	OS-2				

BW- birth weight; GA- gestational age; PMA-postmenstrual age; LSCS - Lower segment Cesarean section, M- Male, F- Female, RDS-Respiratory Distress syndrome, OD- right eye; OS- left eye.

There were fourteen males (58.3%). (Table 2) The mean GA was 32.25 ± 1.32 weeks. The mean BW was 1.47 ± 0.32kg. Systemic high risk factors like RDS (33.4%), anemia (16.7%), septicemia (8.3%) were also noted (Table 3). In our study, 16.7%of cases were of zone 1 ROP, 58.3% zone 2 ROP and 25% were of zone 3(table 4). All 24 babies had stage 3 or more of ROP with or without AP-ROP. Percentage of aggressive posterior ROP was 41.7%. (Table 5)Mean follow-up period was 9.58 ± 1.97 months. (Table 6)

Table 2 Distribution among the cases as per gender

Gender	No.	Percentage
Female	10	41.7%
Male	14	58.3%
Total	24	100.0%

Table 3 Distribution among the cases of Mode of delivery, RDS, medical history and anemia

	No.	Percentage (n=24)
LSCS	20	83.3%
	4	16.7%
Vaginal		
Yes	8	33.4%
No	16	66.6%
Septicemia	2	8.3%
Normal	22	91.7%
Yes	4	16.7%
No	20	83.3%

Table 4: Distribution among the cases of Zone of ROP

Zone of ROP	No.	Percentage
1	8	16.7%
2	28	58.3%
3	12	25.0%
Total (eyes)	48	100.0%

Table 5 Distribution among the cases of AP ROP

AP ROP	No.	Percentage
Yes	10	41.7%
No	14	58.3%
Total	24	100.0%

Table 6: Various statistical variables

Variables	No. patients	Mean	SD
Gestational Age (Weeks)	24	32.25	1.32
Post Menstrual Age (years)	24	36.08	1.61
Birth Weight (Kg)	24	1.47	0.32
F/U (months)	24	9.58	1.97

Primary success was observed in 36/48 eyes (75%). We also found continuation of normal vascular growth into the peripheral retina, without any signs of disease recurrence or progression during the follow up period.(Figure 1) Additional laser treatment was required for 6 patients (12 eyes). Retreatment occurred at a mean of 7.8 weeks after initial IVR treatment (range 6-10 weeks). Treatment success was achieved in these 12 eyes after laser treatment. (Figure 2) Out of 6 babies requiring additional laser ablation (12eyes), 4 babies (8 eyes) had AP-ROP.

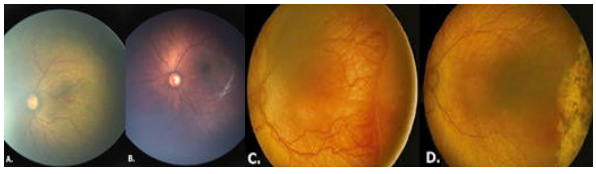

Figure 1 A. OS showing Zone 2, stage 3 AP-ROP with tortuous and dilated blood vessels. Peripheral avascular ridge is seen. B. Resolved ROP with single IVR at 10 months follow-up.

Figure 2 C. OS showing Zone 2, Stage 3 AP-ROP. Peripheral avascular retina with neovascularization noted. D. Secondary treatment success achieved with laser ablation, stable retina at 9 months follow –up.

All study eyes demonstrated attached retina without any signs of adverse outcome such as macular dragging and folds or retinal detachment. No systemic or ocular adverse effects, related to the injection itself or the drug, were observed.

DISCUSSION

Retinopathy of prematurity (ROP) is a vasoproliferative pathologic process that occurs in an incompletely vascularized retina of low birth-weight preterm neonates. The main risk factors for ROP are preterm delivery and low birth-weight. The other risk factors include exposure to varying oxygen concentrations, hypercapnia, anemia, acidosis, chronic lung disease and intraventricular hemorrhage (IVH). [42, 43]

ROP is a biphasic disease, with an initial vaso-obliterative phase characterized by stimulation of VEGF by relative hypoxia in the peripheral avascular retina. This is followed by a vasoproliferative phase characterized by neovascularization [44]. There is only a single burst of VEGF which causes neovascular growth in ROP [45] .This differentiates it from other ocular neovascular diseases such as exudative neovascular age-related macular degeneration (ARMD), which have continual VEGF release. Delayed anti-VEGF treatment, administered when VEGF levels are decreasing, may not be as effective and may promote fibrosis[46]. There is a recent change in protocol in our center to aggressively treat ROP with anti-VEGF at earlier time points. Consequent to this, in our study the overall rate of ROP recurrence requiring additional treatment was 25 percent. This is comparable with previous studies that have reported additional treatment in 13% to 35.4 percent[32,33,40]. During the extended period of vascular growth, elevation in VEGF levels may reactivate ROP, requiring additional anti-VEGF treatment[47].

In terms of safety, anti-VEGF injections appear to cause few cases of retinal detachment or macular temporal dragging. Even in our study, not a single such complication occurred.

Though both anti-VEGF agents enter systemic circulation following intravitreal injection, ranibizumab appears to suppress systemic VEGF for less time with more rapid systemic clearance than bevacizumab. [48, 49] Therefore, ranibizumab is theoretically safer in its systemic profile, with less risk of neurologic deficits or developmental delays. There were no major systemic complications noted in our study.

Another retrospective study found no difference in neurodevelopment between premature infants treated with IVB versus laser at 2 years, although patients requiring rescue therapy for recurrence (laser plus IVB, in either order) did demonstrate a higher incidence of psychomotor and mental impairment. [50]

In our study, mean GA was 32.25 weeks (30-34weeks). This is comparable with other reports which had a mean GA ranging from 30.8 to 32 weeks. [11-13] We had 10 subjects (41.7%) of AP-ROP in this study. The mean GA and BW of APROP subjects (31.8 weeks and 1.445 kg, respectively) were higher than that reported by Sanghi *et al.* (29.75 weeks and 1259.66 gm). Eight babies (80%) of AP-ROP were born before completing 32 weeks of gestation in our study. Sanghi *et al.* encountered 90.9% babies of APROP who were born less than 32 weeks of gestation. [51]

All babies were initially treated with single IVR 0.2 mg injection. The retreatment rate in our series was 25% (12 eyes). However, our retreatment rate was comparable with Hillier R J et al who reported retreatment rate of 20.7%. [52] Indications for retreatment following IV AntiVEGF in ROP are poorly defined. Recurrence of neovascularization and 'plus' disease would seem to be uniformly compelling indications for retreatment. In our series, we found that the need for retreatment arose at a mean of 44.66 weeks' PMA (range 41-48weks), corresponding to 7.8 weeks post-IVR (range 6-10 weeks). Our recurrence window was somewhat earlier than reported by Mintz-Hittner *et al* (mean 51.2 weeks' PMA (range 46–65), corresponding to 16.2 weeks post-IVB).[20] However, we must stress that we have used Ranibizumab while they have opted for Bevacizumab.

Castellanos et al.followed six eyes of ROP patients receiving ranibizumab for three years and found fully vascularized retinas with no fluorescein leakage on angiography in all eyes.[53] However there are also some *conflicting reports in literature.* Huang et al. noted incomplete vascularization without reactivation after ranibizumab treatment in 2.8% of 286 eyes. [33]

The BEAT-ROP study found the full vascularization rate to be 95.7% in 140 eyes. [20] However, there have also been less favorable reports. Wu et al. [32] reported full vascularization in 88.0% of 162 bevacizumab- treated eyes, and Chen et al. [40] reported full vascularization in only 46.4% of 151 ranibizumab-treated eyes. In our study, we noted a full vascularization rate in 75 percent of subjects receiving anti-VEGF treatment.

We investigated the efficacy, anatomical outcomes, and complications associated with intravitreal anti-VEGF ROP treatment using single injection of ranibizumab.

This study has several limitations. First, it was a small retrospective study with a variable follow-up period and without appropriate controls. Second, the study population was limited to Asian patients in a tertiary hospital setting. Lastly, we did not routinely perform fluorescein angiography to document any qualitative interpretation of posterior pole or peripheral vascular maturation following IVR therapy. However, a qualified retina specialist exercised his clinical judgment and expertise while performing thorough fundus

examinations at each follow-up.

In conclusion, we found that IVR achieved stable retinal vascularization with a low rate of complications and fewer recurrences. Ranibizumab appears to achieve similar anatomical outcomes as bevacizumab, without additional risk for major complications such as retinal detachment or systemic side effects. Further prospective, randomized studies with larger sample sizes are required to confirm these observations.

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