Original Article

Comparative Analysis of Intravitreal Ranibizumab versus Laser Therapy for Retinopathy of Prematurity

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Abstract

The therapeutic effects of intravitreal Ranibizumab injection (IVR) and the efficacy of laser photocoagulation for the treatment of retinopathy of prematurity (ROP) are compared. The screening criteria for ROP were infants born with less than 32 weeks gestational period and/or weighed less than 1500 grams or unstable clinical course. After ethical approval from the Institutional Review Board, this retrospective study was conducted. The study considered 1315 infants and an observation was made that 36/42 (85.7%) eyes showed regression of ROP in the IVR group whereas 27/27 (100%) eyes that were treated with laser therapy showed regression of ROP (p=0.09). A considerable discrepancy in habituation of ROP in both groups with 12 eyes (28.6%) has been noted which is showing recurrence of ROP in the IVR group compared to 1 eye (3.7%) in the Laser group (P=0.01. In terms of anisometropia and refractive error, both groups made no notable difference. Squint was found remarkably higher in the laser group (29.6%) than in the IVR group (4.8%) (P=0.01). It was found that treating ROP eyes with laser treatment leads to greater improvement in infants than when treated by IVR. Moreover, a significant recurrence of ROP was discovered after IVR treatment in comparison with the laser treatment.

Keywords: Retinopathy, IVR treatment, Ranibizumab, Vascular endothelial growth factor (VEGF)

Introduction

Blindness occurring in childhood, across the world, is caused mostly by Retinopathy of prematurity (ROP) [1, 2]. Data showed nearly 28300-45600 cases per year worldwide of infants developing irreversible impairment of vision due to ROP [3]. Normal retinal development vasculature is completed when retinal vessels reach the boundary between the retina and ciliary body known as ora Serrata. This phenomena is completed in normal infants by 40 weeks of gestation [4].

The pathogenesis of ROP has been attributed to changes in the amounts of vascular endothelial growth factor (VEGF), insulin-like growth factor I (IGF-I), oxygen, alongside other factors which leads to the atypical growth of blood vessels and cause permanent damage to the retina [5, 6]. A joint statement constituting guidelines for screening of ROP states that preterm infants with birth weight less than1500 grams or less than 30 weeks of gestation and/or with complicated clinical courses must be screened for ROP [7].

For the last few decades, laser photocoagulation has been used frequently for ROP treatment [8]. Diode (810 nm) or argon green (514 nm) laser have been the choice of treatment for avascular retinal ablation as the diode laser has deeper absorption and less risk of induction of cataracts. Treatment is targeted to the entire avascular retina and extends up to the ora Serrata [8, 9]. Unfavorable visual and structural outcomes were found to be reduced with treatment [10, 11]. Other studies also prove the safety and efficacy of laser suggesting that laser photocoagulation is an effective treatment for ROP [12, 13].

Dysregulation of VEGF is considered one of the underlying mechanisms for ROP [14]. Injection of anti-VEGF agents like Ranibizumab, Bevacizumab, and Aflibercept into the vitreous is a popular strategy for management of diseases associated with vaso-proliferation and hyperpermeability in adult ophthalmologic practices [3].

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The largest clinical trial of anti-VEGF treatment in preterm infants was confucted to put in comparison the efficacy of intravitreal bevacizumab with laser therapy in the US population [15]. Later on, Sato *et al*. showed the leak of Bevacizumab from the vitreous into the general circulation, thereby decreasing the systemic levels of VEGF in infants after intravitreal Bevacizumab (IVB) [16].

Results have differed in most of the studies with few showing efficacies of Ranibizumab alone to control ROP and others showing a significant number of eyes with recurrence of the diseases [3, 17]. Some studies have also shown the need for a second treatment regimen with laser [18]. Available data is controversial suggesting one of the two strategies is superior to the other in different studies.

Materials and Methods

Design and Enrollment

This retrospective study was carried out after ethical approval from the Institutional Review Board. Infants were screened for ROP in the neonatal intensive care unit of XXX. Infants included in the study were enrolled for a period of 7 years, from January 2011 to December 2017. Infants born after a gestational period fewer than 30 weeks and/or weighed less than 1250 grams were the screening criteria for ROP based on the guidelines by the Canadian Pediatric Society [19]. Three experienced ophthalmologists examined each infant independently and the eligibility of their inclusion for the treatment was confirmed by all of them.

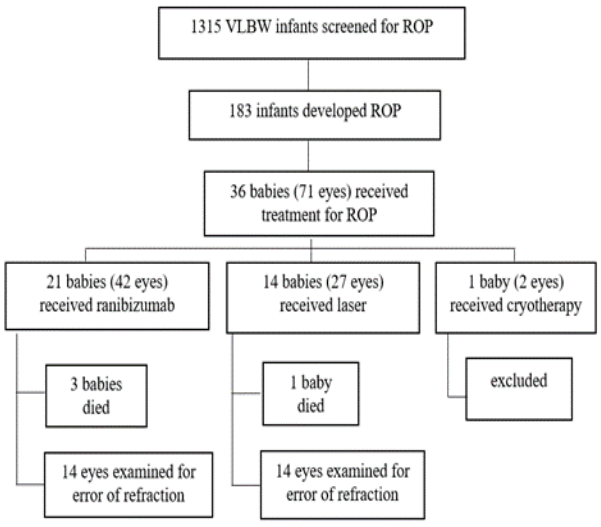

Figure 1. Flow chart for the study Cohort

Treatment

Diagnosis and treatment performed in the study were as per the early treatment of ROP and international classification of ROP [10, 19].

Medicament indicated for type 1 ROP, which is defined as the development of any of the following findings:

ROP zone 1 with any stage with plus disease ROP zone 1 with stage 3 with no plus disease ROP zone 2 stages 2 or 3 with plus disease.

From January 2011 to June 2014, laser therapy was the standard of care, from July 2014 to December 2017; infants were treated with IVR followed by either a second dose of IVR or laser therapy if ROP progressed. Laser photocoagulation was carried out under sedation with or without general anesthesia in the neonatal intensive care unit or the operating room. An indirect infrared diode laser (Iridix; Quantel-Medical, Cournon d'Auvergne Cedex, France) (810 nm) was utilized to apply photocoagulation by a 20 or 28 diopter condensing lens. The initial laser was set at a power of 150-500 mW for 0.1 to 0.2 seconds, with the aim to achieve a threshold burn. Confluent or near-confluent laser treatment was applied to the avascular retina up to the ora serrata for 360°. Photocoagulation for the peripheral retina was done with sclera indentation. After photocoagulation, topical steroid and cycloplegic mydriatic were administrated for one week.

Intravitreal injection of Ranibizumab was done under topical anesthesia using lid spectrum in the neonatal intensive care unit. Standard aseptic eye preparation with 5% betadine was used during the procedure. The dose of Ranibizumab used was 0.25 mg/0.025 mL, it was administered with 30- a gauge needle, 1.25 mm from the limbus. If a follow-up eye exam showed recurrence or no regression of ROP, another dose of IVR was given and the infant was booked for laser photocoagulation in case of no regression or recurrence as recommended by the ophthalmologist.

Follow-up

A day after the procedure examinations were conducted on infants treated with IVR or laser photocoagulation and weekly thereafter. The treatment unit made follow-ups and examined all treated infants for at least 12 months until total regression of ROP and assessed for refraction errors as outpatients. The primary outcome measured was regression of ROP, secondary outcomes measured wereROP recurrence, need for a second dose of Ranibizumab, need for the second round of laser treatment, refraction errors, severe myopia, squint, astigmatism, and anisometropia. Regression of ROP and vascularization was assessed with dilated fundus examination using indirect ophthalmoscopy. Initial cycloplegic retinoscopy was performed to evaluate retraction during the follow-up period.

Statistical Analysis

Data collection, descriptive statistics, and analysis were computed in spreadsheet and statistical software (SPSS 25 and Microsoft Excel). Detailed analysis was expressed in mean ± SD for normally distributed variables. The Chi-square was applied to collate the outcomes between Ranibizumab treated

group and the laser-treated group. For statistical significance, a p-value of less than 0.05 was considered.

Results and Discussion

A total of 1315 VLBW infants were screened for ROP from January 2011 till December 2017. Among these 183 infants (13.9%) developed ROP. In thirty-six infants, 71 eyes received treatment for ROP. Twenty-one babies (42 eyes) received Ranibizumab, 14 babies (27 eyes) underwent laser photocoagulation and 1 baby (2 eyes) received cryotherapy **(Table 1)**. For further analysis, 69 eyes from 35 infants were included, excluding the cryotherapy-treated infants. IVR group consisted of 42 eyes from 21 infants who received Ranibizumab treatment and the laser group consisted of 27 eyes from 14 infants who underwent laser treatment **(Figure 2)**.

Patient Characteristics

The characteristics of the 35 infants included in the 2 groups are shown in **Table 1**. No notably statistical difference was depicted in the mean gestational age [Group I: 25. 48± 2.3 and group II: 26.26± 2.3 weeks (p =0.219), mean birth weight [Group I: 785.46 ±175.81 and group II: 786.67 ±164.67 grams (p = 0.381)], weight for gestational age (p = 0.148) and gender (p= 0.518) among the two groups **(Figure 3)**.

There were no remarkarble differences between the patients of the two groups in terms of gender, mean values of Apgar score at 5 minutes and BPD, p<0.05, however, surfactant, BPD, sepsis, PVL, IVH, and PMA when treatment was commenced was not statistically different among the two groups, p>0.05.

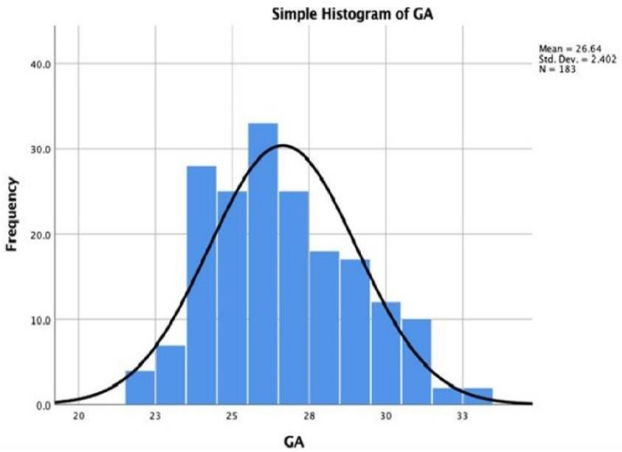

Figure 2. Representation of Gestational Age distribution

Table 1. Baseline characteristics of infants who received Ranibizumab and laser

Patients Characteristics	Statistical Analyses	Ranibizumab (21 infants)	Laser (14 infants)	P value
Gestational Age	Mean ± SD	25.48 ± 2.3	26.26 ± 2.3	0.247
	Range	22-31	24-31	
Gender	Male n(%)	9(42.9%)	8(57.14%)	0.03*
	Female n(%)	12(57.1%)	6(42.8%)	
Birth weight	Mean ± SD	785.46 ±175.81	786.67 ± 164.67	0.26
Weight to Gestational Age	AGA n(%)	13(61.9%)	8(38.1%)	0.15
	SGA n(%)	6(28.6%)	4(19.0%)	
	LGA n(%)	2(4.8%)	2(9.5%)	
PMA at start of treatment	Mean ± SD	38.67 ±2.564	42.00 ±2.526	0.36
APGAR at 5 min	Mean ± SD	7.14 ± 0.51	8.0 ± 1.07	0.03*
PDA	n(%)	12(57.1%)	9(64.2%)	0.11
BPD	Moderate n(%)	6(28%)	5(35.7%)	0.005*
	Severe n(%)	9(42.9%)	5(35.7%)	
Surfactant	0 n(%)	1(4.8%)	1(3.7%)	0.33
	1 n(%)	4(19.0%)	4(29.6%)	
	2 n(%)	8(38.1%)	2(14.8%)	
	3+ n(%)	6(28.6%)	5(37.0%)	
Gram positive bacteremia	n(%)	11(52.4%)	9(63.0%)	
Gram negative bacteremia	n(%)	6(28.6%)	5(33.3%)	

IVH (grade 3 or 4)	n(%)	6(28.6%)	6(42.2%)	<0.001
PVL	n(%)	4(19%)	1(7.4%)	0.29

Bold values indicate statistical significance (*) p<0.05, SGA= small for gestational age, AGA= Appropriate for gestational age, LGA= Large for gestational age, PMA= Premarket Approval, APGAR= Appearance, Pulse, Grimace, Activity, and Respiration, PDA= persistent disease activity, BPD= Biparietal diameter, PVL= Periventricular leukomalacia, IVH= Intraventricular hemorrhage.

Table 2. Comparative table showing various outcomes of both the treatment strategies

Treatment Groups	Ranibizumab	Laser	CI	P value
Sample Type	(42 eyes)	(27 eyes)		
Regression n (%)	36 (85.7%)	27(100%)	(-0.22, 0.02)	0.09
Recurrence n (%)	12(28.6%)	1(3.7%)	(0.09, 0.68)	0.01*
Required Second IVR n (%)	8(19%)	0%	(0.04, 0.34)	0.02*
Required Second Laser n (%)	10(23.8%)	0%	(0.07, 0.40)	0.01*
Error of Refraction Mean + SD	-0.97+5.09	0.18+4.7	(-4.60, 2.32)	0.51
Severe myopia Mean + SD	3(7.1%)	3(11.1%)	(-0.86, 0.82)	0.97
Astigmatism n (%)	10(23.8%)	14(51.9)	(-0.52, 0.12)	0.21
Squint n(%)	2(4.8%)	8(29.6%)	(-0.73, -0.09)	0.01*
Anisometroia n(%)	2(4.8%)	7(25.9%)	(-0.67, 0.02)	0.06

Bold values indicate statistical significance (*) p<0.05.

- *Regression of ROP*

It was observed that in the laser group there was regression of ROP in all the eyes (27 eyes; 100%) treated with laser photo-coagulation. However, in the IVR group, eyes treated with a single dose of intravitreal Ranibizumab showed regression in 36 out of 42 eyes (85.7%) (P=0.09).

- *Recurrence of ROP*

There was a significant statistical difference in the recurrence of ROP in the study groups with the IVR group showing a higher rate of recurrence. It was found that 12 eyes from the IVR group (28.6%) showed recurrence of ROP after a single dose injection of Ranibizumab whereas in the laser group only 1 eye (3.7%) showed recurrence of ROP (p = 0.01).

- *Additional Post-Baseline Treatments*

As for post-baseline treatment is concerned, 8 eyes from the IVR group (19%) required a second dose of IVR but no infants from the laser group received IVR (p= 0.02). This shows that a significant number of patients in the IVR group required a second dose of IVR as compared to no patient who required a second round of treatment in the laser group **(Table 2)**.

It was further observed that 10 eyes (23.8%) required laser treatment after initial treatment with IVR which was significantly higher than the laser group wherein no infants required a second dose of laser (p=0.01) **(Table 2)**.

Refractive Analysis and other Parameters

Cycloplegic retinoscopy was used for measuring refractive error. Fourteen eyes were examined for errors of refractions in the IVR group (14 infants were excluded from the refractive analysis in the IVR group due to loss of follow-up of 11 infants and death of 3 infants). Cycloplegic refraction was performed in 14 eyes in the laser group (6 infants lost the follow-up and one infant died). For refractive errors, there was no significant difference between both groups with a mean error of refraction at 12 months to 18 months of age -0.97 ± 5.09 for the IVR group and 0.18 ± 4.67 for the laser group (p=0.51) **(Table 2)**. It was observed that among all participant's highest percentage of ROP patients were observed in zone 3 (46.44%) and 4 (45.90%) while the lowest number of participants were observed in zone 1 (38.30%).

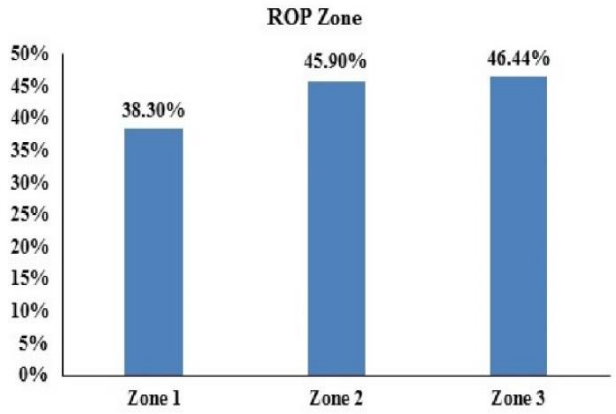

Figure 3. Percentage representation of participants lie in each zone. Zone 1 indicates ROP zone 1 with any stage with plus disease 2, zone 2 indicates ROP zone 1 with stage 3 with no plus disease 3 and zone 3 carry ROP stage 2 or 3 with plus disease

Significant myopia (refractive error -6 or more) was observed in 3 eyes (7.1%) in the IVR group and 3 eyes (11.1%) in the laser group (p=0.97). Astigmatism was found in 10 eyes (23.8%) in the IVR group and 14 eyes (51.9%) in the laser group, the difference in cases among both the groups was non-significant (p=0.21).

Anisometropia (difference of 2 or more diopters between both eyes) was also found in both the treatment groups with more eyes showing anisometropia in the laser group but the difference in incidence was non-significant when compared among both groups [2 (4.8%) eyes in IVR group and 7 (25.9%) in laser group (p=0.06)].

Notable disparity was observed in the occurrence of squint among the two groups, with 2 eyes (4.8%) developing squint in IVR treated group and 8 eyes (29.6%) in the group treated with laser (p=0.01).

Laser ablation of the avascular retina can cause an incline in the levels of VEGF and further regression of neovascularization [20]. Various studies including an ETROP study confirmed from its analysis of six years that laser treatment is beneficial for type 1 ROP at the high-risk pre-threshold stage [8, 11]. Recently, in line with the fact that VEGF plays a major role in angiogenesis and vascular growth in the retina, anti-VEGF agents for the treatment of ROP came into focus. Initially, bevacizumab was evaluated in a multi-center trial and a few other studies as the primary treatment for ROP; later on, Ranibizumab was introduced with prospective benefits due to its short half-life in serum along with less penetration in the systemic circulation [15, 18, 21-24]. However, evidence supporting which therapy out of laser photocoagulation and intravitreal injection of Ranibizumab is a better option is not clear with many studies showing controversial data. Therefore, in the given case, we have carried out a comparative analysis of both treatment strategies. Laser photocoagulation and intravitreal Ranibizumab injection focusing in terms of regression, recurrence, refractive errors, and other side effects.

We observed that during the duration of the study, 85% of infants with type 1 ROP in the IVR group treated with a single dose of Ranibizumab showed regression of ROP, the better response was observed in the laser-treated group with all the infants (100%) showing regression of ROP. However, the difference was not significant but it indicated a better recovery in the group treated with laser. Our study was supported by Lyu *et al.* who reported that both the treatment strategies resulted in regression of type 1 ROP in a nearly similar proportion of eyes [25]. Other studies conducted in Turkey and China also showed that the initial regression of ROP observed in both single-dose IVR and laser treatment infants was comparable [17, 26].

In terms of recurrence of ROP, it was observed that the group treated with a single dose of IVR had a significantly high incidence of recurrence in comparison with the group treated with laser. Our results corroborated with Zhang *et al*. who conducted a prospective randomized controlled clinical trial enrolling 50 infants and concluded that even though IVR resulted in regression of ROP to an extent and also promoted peripheral retinal vessel vascularization, a considerable proportion of treated infants (52%) showed recurrence of the disease when compared to those treated by laser. They suggested that single-dose monotherapy of IVR is not recommended alone for treating severe ROP [17]. Two studies published in the year 2013 did not report any recurrence of ROP after treatment with IVR [27, 28]. However, a later study by Wong *et al*., 2015 reported nearly 83% recurrence of ROP post-treatment with Ranibizumab [29]. Data reported by Gunay *et al*., 2017 of a retrospective review including 134 infants with type 1 ROP in turkey also showed that recurrence of ROP was in 50% of cases treated with IVR and only 1.7% treated with laser photocoagulation. The one reason for the increased rate of recurrence after initial injection with Ranibizumab might be that it is an antibody fragment with a short half-life and is rapidly cleared from the eyes [30]. This suggests that considering the shorter durational suppression of VEGF by Ranibizumab, there could be a frequent need for follow-ups and possible further treatment if recurrence is diagnosed. Another important conclusion is drawn by Feng *et al*., and other studies was that the aggressiveness of ROP also determines the rate of recurrence after IVR treatment [31]. High rates of recurrence were found in the zone I ROP as compared to zone II ROP post-treatment with Ranibizumab which could be caused bt its much-time requirement to attain full vascularization, increasing the probability of an increase in VEGF levels consequently [32]. We can infer that IVR treatment in severe ROP did not eradicate the possible risk of late reactivation of the disease, on the contrary laser offers much better results with less probability of recurrence.

We further observed that as for post-baseline treatment is concerned, 19% of patients in the IVR treated group required a second dose of IVR, and 23.8% of patients required laser treatment after initial treatment with IVR. This difference in the need for the second round of treatment was significantly higher in IVR treated group than in the laser-treated group wherein no patient required a second round of treatment. The babies in the IVR group had more severe disease, as 95% of eyes had plus disease compared to the laser group (40%), which could be the possible reason for higher recurrence in the IVR group. As discussed above treatment with a single dose of Ranibizumab has a higher rate of recurrence, this goes in line with the finding that such infants needed a second round of treatment either with IVR or laser. Many other reports supporting our findings have also shown a second treatment schedule either with Ranibizumab or laser post-treatment with IVR [17, 18, 26]. Tong *et al*., reported that 0.3mg of Ranibizumab had a recurrence rate of 51% (82 out of 160 eyes) [33]. In a RAINBOW randomized control, clinical trial by Stahl *et al*., patients with ROP received 0.2mg Ranibizumab, 0.1mg Ranibizumab, or laser therapy. The outcomes of the study showed that 0.2mg Ranibizumab had greater clinical efficacy compared to the other two methods. Structural outcomes were better in this group compared to the other two groups and no adverse events are reported among the three groups [34]. Recurrence of ROP could be dose and severity-dependent. Furthermore, the type of VEGF inhibitor is also likely to affect the rate of recurrence [35].

Both anti-VEGF treatment and laser photocoagulation have been associated with the occurrence of myopia. BEAT-ROP study has shown that myopia was found to be significantly higher in both the treatment strategies [33]. The study by Hwang *et al*. showed a lower degree of myopia in the Bevacizumab treated group as compared to laser treatment [34]. As for Ranibizumab is concerned, very less data is available on refractive errors. Kabatas *et al*., 2017 compared intravitreal Bevacizumab, intravitreal Ranibizumab with laser photocoagulation for treatment of type 1 ROP and observed myopia in all the groups [36]. All the groups showed myopia in a nearly similar proportion. Similar to this study, we did not find any significant difference in refractive errors and severe myopia in both the treatment groups. Although many studies have shown myopia associated with ROP treatment but factors affecting it are not well explored and need further investigation. There is no significant difference in the incidence of astigmatism in this study which was similar to findings observed by Kabatas *et al*. It was reported that children treated with the laser have high incidences of anisometropia [37, 38]. In our study, there was no significant differences in the number of eyes showing anisometropia in both the treated groups.

Various studies have reported a high incidence of squint in the eyes post-treatment with laser. Stoica *et al*., in a study, evaluated the visual outcomes after laser treatment; found that 46% of patients showed the prevalence of strabismus [39]. It was reported by two other studies also that 50-55% of eyes showed squint after treatment with laser [40, 41]. These findings supported our data which showed a significantly high number of eyes showing squint after laser treatment as compared to IVR.

Conclusion

In this study, we showed that regression of ROP when treated with IVR was less than laser photocoagulation and a substantial number of infants showed recurrence of ROP after a single dose of IVR. However, the sample size of the study is too small to obtain a definite conclusion. Moreover, many infants from the group treated with IVR required a second dose of IVR, owing to high recurrence, relative to laser photocoagulation or both. The severity of ROP was greater in the IVR group, which could be suggestive of these findings. Therefore, more studies are required with a greater sample size that can compare outcomes in groups that are homogenous in terms of the severity of the disease. Greater sample size may also compensate for the loss of follow-up.

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