ORIGINAL ARTICLE

Retinopathy of Prematurity: A Short Term Follow up Study of Effectiveness of Intravitreal Anti Vascular Endothelial Growth Factor (Anti VEGF) [Ranibizumab] as an Initial Adjuvant to Laser Photocoagulation in the Management of Aggressive Posterior Retinopathy of Prematurity (AP-ROP) at a Tertiary Care Centre in North India

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ABSTRACT

Background: The present study had been undertaken to assess the role of intravitreal anti vascular endothelial growth factor (Anti VEGF) [Ranibizumab] as an adjuvantto laser photocoagulation as an initial standard of care treatment modality for Aggressive Posterior Retinopathy of Prematurity (AP-ROP) at a tertiary care centre of North India.

Material and Methods: The present long-term study (of 48 months duration), initiated in January 2018had been designed to assess 56 neonates suffering with AP-ROP (with involvement of both eyes namely, 112 eyes) and an intermediate data analysis across a timeline of 28 days during the study. All the participant neonates were diagnosed of suffering from Aggressive Posterior Retinopathy of Prematurity (AP-ROP) on screening throughindirect ophthalmoscopy at a tertiary care centre of North India and the participant neonates were randomly distributed in two groups wherein one group selected was put on an initial intravitreal injection (IVR) of Anti-VEGF, Ranibizumab(0.2 mg in 0.025 ml) and serially monitored for requirement of quanta of laser spots with subsequentLaser Photocoagulation (LP) and the other group selected was given LP, the requirement for quanta of laser spots being identified for both the groups through indirect ophthalmoscopy, an analysis that has an inherent subjective bias. Such an observer bias can be minimised using objective imaging through Fundus Fluorescein Angiography (FFA), though the same had operational hindrances and subsequently was not employed the present study. Moreover, the subjective bias was minimised since the same was used in both study group arms. The regression of signs of AP-ROP post injection were assessed and any crossover treatment due to failure of resolution or worsening of signs was documented.

Results: The short-term follow-up of the two groups inclusive of the group with AP-ROP managed with initial IVR along with requirement of quanta of laser spots with subsequent LP and the other group given primarily LP was carried out. The infants in both the groups were followed up and the proportion of infants with resolution of symptoms at Day 1 ($p<0.001$), Day 7 ($p=0.005$), Day 14 ($p<0.001$) and Day 28 ($p=0.017$) was significantly high in the IVR with subsequent LP group as compared to that observed in singular LP. The Laser Photocoagulation beyond Zone 1 at day 28th for infants (from day 1 of start of therapy) in IVR group as well. It was observed that the number of laser spots in need of LP in the IVR arm was less (mean 1,469.41) as compared to that observed in infants receiving singular LP (mean 3,068.48) and the difference was highly significant ($p<0.001$). It was observed that 2 diseased eyes (1.79%) developed tractional retinal detachment after Ranibizumab. Moreover, it was observed that 6 disease eyes (5.35%) had to switch over and were given subsequent crossover treatment with Ranibizumab post 1 week of injection due to failure of resolution of signs of AP-ROP post Laser Photocoagulation (LP).

Conclusion: It was observed that intravitrealanti vascular endothelial growth factor (Anti VEGF) Ranibizumab seems to provide comparable and appreciable resolution of symptoms post IVR therapy and implicates the possibility of arrest of progression of AP-ROP (inclusive of neovascularisation) to sight threatening complications as compared to the results of singular laser photocoagulation, an observation that could probably be due to anti-neo vascular action of Anti VEGF,

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Ranibizumab. The said management protocol of an Anti VEGF in AP-ROP seems to halt the basic pathophysiology the disease process, increasing the size of viable vascular retina with two potential advantages namely, a delayed need of Laser Photocoagulation (LP) with subsequent less stress on the neonate and a decrease in surface area of the neural tissue of retina to be lasered that could lead to better visual outcomes for the child.

Keywords: Aggressive Posterior Retinopathy of Prematurity (AP-ROP); Laser Photocoagulation; Ranibizumab; Retinopathy of Prematurity

INTRODUCTION

Aggressive posterior retinopathy of prematurity (AP-ROP) is a severe and uncommon form of retinopathy of prematurity (ROP) which is characterized by fast progression to an advanced stage with flat neo vascularisation in zone 1 or zone 2[1,2]. Previously, AP-ROP has been referred to as type II ROP or rush-type ROP[3]. In the year 2005, revised report of the International Committee for the Classification of Retinopathy of Prematurity, type II ROP or rush-type ROP has been termed as AP-ROP, that has been characterised by (1) a more posterior location, (2) rapid progression, rather than through the classic stages 1–5 and (3) poor prognosis despite early treatment[4]. AP-ROP generally occurs in premature (gestational ages [GA] <28 weeks) and low-birth weight (BW) infants (<1,000 g)[5].

Although the pathogenesis of ROP has still not been completely appreciated, it has been proposed and hypothesised that dysregulation of production and release of vascular endothelial growth factor (VEGF) may lead to abnormal vasculogenesis and induce neovascularization contributing significantly to pathogenesis of this disorder[6,7]. Subsequently, intravitreal injections of the anti-VEGF have been designed, approved and used for management of ROP[8-10]. Ranibizumab (Lucentis; RG-3645; rhuFab V2; VEGF antibody fragment) is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A) [11]. Laser photocoagulation has been the standard of care treatment of ROP for the last two decades, though a large area of peripheral retina is destroyed with antecedent dysfunction of neural retinal tissue during the ablating laser procedure[12,13]. In this background, the present study was designed to assess the role of intravitreal anti vascular endothelial growth factor (Anti VEGF) [Ranibizumab], Intra Vitreal Ranibizumab (IVR), as an adjuvant and first line of treatment preceding laser photocoagulationfor the preterm infant as an initial standard of care treatment modality for Aggressive Posterior Retinopathy of Prematurity(AP-ROP)in Indian perspective.

MATERIALAND METHODS

Screening

Screening was done in all preterm infants who were born before 34 weeks of gestation and/or < 1,750 grams birth weight; as well as in neonates of 34-36 weeks of gestation weigning 1,750- 2,000 grams birth weight if they had risk factors for retinopathy of prematurity. The first retinal examination was performed not later than 4 weeks of age or 30 days of life in infants born ⩾ 28 weeks of gestational age. Infants born < 28 weeks or < 1,200 grams birth weight were screened early, by 2-3 weeks of age, to enable early identification of Aggressive Posterior Retinopathy of Prematurity (AP-ROP). All the infants who were screened for ROP and diagnosed as having AP-ROP were included in the study. The parents were informed about the treatment options and potential side effects and infants were categorised and segregated into two groups inclusive of the group with AP-ROP managed with initial IVR along with requirement of quanta of laser spots with subsequent LP and the other group given primarily LP after getting due assent. The grading and severity of AP-ROP was assessed as guidelines laid down in International Classification of Retinopathy of Prematurity (ICROP) and follow up was done according to guidelines of American Academy of Paediatric Ophthalmology (AAPO)[1,14].

Participants

56 neonates who were diagnosed as having AP-ROP based on the screening were included in the study. The study recruitment spanned over a period of 1 year from January 2018 to January 2019 wherein the patients recruited in each ROP clinic were distributed into two segregated study groups namely, AP-ROP managed with initial IVR along with requirement of quanta of laser spots with subsequent LP and the other group given primarily LP through simple random sampling. Each recruited infant was assessed on follow up at Day 1, Day 7, Day 14, Day 21 and Day 28. All the perinatal risk factors such as low birth weight, history of prematurity, gestational age, post conception age, oxygen requirement, septicaemia,

blood transfusions, intracranial haemorrhage and respiratory distress were tabulated and documented.

Procedure

Under aseptic precautions in sterile Ophthalmology Operation Theatre (OT), 35 infants of post gestational age 4-6 weeks were given intravitreal Ranibizumab (Lucentis, Genentech, San Francisco and Razumab, Intas, India) 0.2 mg in 0.025 ml with a 30 G needle 1.5 mm from limbus in inferotemporal quadrant[15]. The said injected eye was patched with antibiotic ointment and dilated fundus examination was done on day 1, 7,14, 21 and 28. Only one eye was injected in a sitting and the child was called for injection in the second eye after 1 day as per the laid down hospital protocol.

21 infants underwent laser photocoagulation of peripheral avascular retina of both eyes in one sitting in the Eye OT under sterile conditions in presence of a paediatrician and anaesthetist. The mothers were asked to feed the babies before starting the laser and after completion of laser of both eyes and children were followed up on day 1, 7, 14, 21 and 28 as per protocol. The treatment was classified as failure if there was non-regression of neovascularisation or recurrence of disease was observed. All eyes (belonging to both groups) so recruited were given laser photocoagulation irrespective of treatment given were lasered at the end of 4th week.

Ethical Statement

An approval from institute ethical committee was obtained, in accordance with the Declaration of Helsinki. Informed consent was taken from all patients for undergoing procedure and benefits as well as side effects of each modality of treatment were explained in detail.

Statistical Analysis

Appropriate parametric and non-parametric statistical tests were used in the study. Data was coded in Microsoft Excel and all statistical calculations were done in it. Descriptive statistics were used along with analysis with Chi square and independent sample t test.

RESULTS

A total 112 eyes of 56 infants with AP-ROP were included in the study which included randomly distributing the intervention i.e., IVR followed by LP and LP alone with subsequent evaluation of the protocol through indirect retinoscopy. A total of 70 eyes received Intravitreal Ranibizumab [IVR] (62.5%) and 42 eyes underwent Laser Photocoagulation [(37.5%). At baseline both the groups i.e., IVR followed by LP and LP alone were comparable so that no significant difference could be appreciated in terms of birth weight (p=0.353), gestational age (p=0.487) and post-gestational age (p=0.266). The birth weight of AP-ROP ranged from 7,12-1,402 grams with a mean weight of 1,064.79 ± 219.63 gm. The gestational and post gestational age of AP-ROP infants ranged from 23-29 weeks (25.75 ± 2.20) and 23-34 weeks (27.64 ± 3.71), respectively.

Table 1: Comparison of gestational age, birth weight, and post-gestational age at treatment between the two study groups

	IVR injection followed by Laser Photocoagulation	Laser Photocoagulation	Total	T test with P value
Number of eyes	70 (62.5%)	42 (37.5%)	112 (100%)	
Birth weight	1073.43 (221.16)	1050.38 (221.69)	1064.79 (219.63)	T=0.037 P=0.353
Gestational age	25.74 (2.18)	25.76 (2.27)	25.75 (2.20)	T= 0.031 P= 0.487
Post-gestational age	27.89 (3.72)	27.24 (3.75)	27.64 (3.71)	T= 0.628 P= 0.266

* All eyes were in Aggressive Posterior Retinopathy of Prematurity (AP-ROP) stage of the disease

In the present, the additional clinical features of oxygen requirement in participating neonates with AP-ROP was present in 54 (96.4%), blood transfusions were given in 31 (55.3%) and septicaemia was noted in 18 (32.1%). Supplemental oxygen was given for a mean period of 17 days (Range 10-38 days).

After intervention, the infants in both the groups were followed up and the proportion of infants with resolution of symptoms at Day 1 ($p<0.001$), Day 7 ($p=0.005$), Day 14 ($p<0.001$) and Day 28 ($p=0.017$) was observed to be significantly high in the IVR followed by LP as compared to the singular LP group. In the present study, the combined IVR and LP group received Laser Photocoagulation (LP) as well beyond Zone 1 at day 28th, wherein it was observed that the number of laser spots needed in the said group was less (with a mean of 1,469.41) as compared to those infants receiving LP alone since Day 1 (with a mean of 3,068.48) and the difference so observed was statistically significant ($p<0.001$). It was observed that 2 diseased eyes (1.79%) developed tractional retinal detachment after Ranibizumab. Moreover, it was observed that 6 disease eyes (5.35%) had to switch over and were given subsequent crossover treatment with Ranibizumab post 1 week of injection due to failure of resolution of signs of AP-ROP post Laser Photocoagulation (LP). The patients who developed tractional retinal detachment were referred to higher centres accordingly.

Table 2: Resolution of symptoms with IVR followed by Laser Photocoagulation (LP) and Laser Photocoagulation alone and comparative evaluation of Laser spots required in the two groups at 4th week

	IVR followed by LP	Singular LP	Chi square P value
Day 1	40 (55.55%)	6 (14.2%)	19.920 ($p<0.001$)
Day 7	62 (88.5%)	22 (52.3%)	7.781 ($p=0.005$)
Day 14	62 (88.5%)	24 (57.14%)	14.546 ($p<0.001$)
Day 28	66 (94.2%)	30 (71.4%)	5.621 ($p=0.017$)
Total no of Laser spots at 4th week	1,469.41 (356.12) Range of 987-1913	3,068.48 (445.05) Range of 1,923-3,456	T=11.356 P<0.001

DISCUSSION

In the present study, the group with Intravitreal Anti Vascular Endothelial Growth Factor (Anti-VEGF), the monoclonal antibody), Ranibizumab, followed by Laser Photocoagulation (LP) exhibited significantly higher solution of changes in ROP as compared to that seen in the group that was subjected to LP alone and such a difference remained significant that could be appreciated through Day 1, Day 7, Day 14 to Day 28 as well, implicating a potential role of combined/hybrid Intravitreal Ranibizumab therapy along with Laser Photocoagulation (LP) [IVR-LP hybrid](vis-à-vis LP alone) in such a disease process of Aggressive Posterior Retinopathy of Prematurity (AP-ROP), an observation that could appreciated at such a short-term follow-up of 1-month.A widely quoted previous study with another anti-VEGF injection i.e., BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) has also documented similar improved outcomes with intravitreal injection of bevacizumab (IVB) with LP as compared to that observed in Laser Photocoagulation alone. This present study comparatively assessed primarily the effects of the management protocol of IVR-LP hybrid as compared to that observed with LP alone along Zone 1 of Retinopathy of Prematurity (ROP)[16]. Zhang et al (2017) in their study comparing IV Ranibizumab and Laser photocoagulation documented comparable effectiveness for both treatments of IVR-LP hybrid and singular LP[17]. Although IVR appears to regress ROP to certain levels and continues to promote the vascularisation of peripheral retinal vessels, a substantial proportion of infants

developed recurrence of ROP after a single-dose IVR. Therefore, IVR is not recommended as a single-dose monotherapy for Zone II treatment-requiring ROP[18]. In the present study, the IVR primary therapy was augmented with Laser Photocoagulation at Day 28th, with subsequent reduction in dose of laser in terms of number of spots applied in each eye as was documented in IVR-LP hybrid therapy group (1,469) as compared to that observed in the Laser Photocoagulation Monotherapy group (3,068) [p<0.001]. The present findings of the study underscore the fact that the hybrid therapy ofintravitreal injection of Anti-Vascular Endothelial Growth Factor (Anti-VEGF) with subsequent decreasing demand for Laser Photocoagulation (documented through decreased number of laser spots) has the potential of decreasing the necessity of LP leading to reduced chances of complications that are antecedent to Laser Monotherapy namely, regression of new vessels by ablating peripheral retina ischemic areas and tractional retinal detachment[19,20].

Limitations of the present study

The present study has inherent limitations of small sample size with short-term interim analysis of the data follow-up of the participant population. It is planned to follow the recruited population longitudinally[21].

CONCLUSION

It was observed that the combinatorial intravitrealanti vascular endothelial growth factor (Anti VEGF) Ranibizumab along with laser Photocoagulation, the Hybrid IVR-LP, seems to provide comparable and appreciable resolution of symptoms post IVR therapy and implicates the possibility of arrest of progression of AP-ROP (inclusive of neovascularisation) to sight threatening complications as compared to the results of singular laser photocoagulation, an observation that could probably be due to anti-neovascular action of Anti VEGF, Ranibizumab. The said management protocol of an Anti VEGF in AP-ROP seems to halt the basic pathophysiology the disease process, increasing the size of viable neurovascular retina with two potential advantages namely, a delayed need of Laser Photocoagulation (LP) with subsequent less stress on the neonate and a decrease in surface area of the neural tissue of retina to be ablated through laser that could lead to better visual outcomes for the child.

However, the findings of the present study need to be supplanted by long-term follow-up of recruited patient groups, assessing recurrence of the disease process along with antecedent complications like tractional retinal detachment and myopia and would add on to present prevailing knowledge Aggressive Posterior Retinopathy of Prematurity (AP-ROP), giving better insight with clinical applicability.

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