Special Focus on Retinopathy of Prematurity, Original Article

Outcomes of early versus deferred laser after intravitreal ranibizumab in aggressive posterior retinopathy of prematurity

Anil Babanrao Gangwe, Deepshikha Agrawal[1], Aashish Kumar Gangrade[2], Swapnil Madhukar Parchand, Deepanshu Agrawal, Raj Vardhan Azad[3]

Purpose: The aim of this study was to report the treatment outcomes of early and deferred laser in infants of aggressive posterior retinopathy of prematurity (APROP) after initial treatment with intravitreal Ranibizumab (IVR). **Methods:** In a prospective, randomized, interventional study, infants with APROP received IVR (0.25 mg) and were randomized into two groups prior to laser. Laser was done at 1 week (group 1) or at 6 weeks or earlier if there was a recurrence of plus disease (group 2). The structural outcome, number of laser spots, duration of laser procedure and refractive error at 6 months were compared. Favorable structural outcome was defined as, complete regression of disease at 6 weeks after laser. **Results:** 63 eyes of 32 infants with APROP were enrolled. Mean gestational age (GA) and birth weight (BW) were 30.2 ± 2.3 weeks and 1294 ± 372.8 grams respectively. GA, BW, and disease severity were comparable at baseline. 27 (90%) eyes in group 1 and 29 (93.5%) eyes in group 2 had favorable structural outcome ($P = 0.61$) at 6 weeks after laser. Eyes in group 2 (2149.8 ± 688.7) required lesser number of laser spots than group 1 (2570.8 ± 615) ($P = 0.01$). At six months, more eyes in group 1 had myopic refractive error (Mean spherical equivalent: –1.0D ± 1.3) than those in group 2 (Mean spherical equivalent: 0.5D ± 1.9) ($P = 0.002$). **Conclusion:** Infants with APROP receiving IVR have comparable structural outcomes after an early or deferred laser. Moreover, eyes undergoing deferred laser require less number of laser spots and have a less myopia at 6 months after laser.

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Aggressive posterior retinopathy of prematurity (APROP) is an uncommon, severe and rapidly progressive form of retinopathy of prematurity (ROP). In the absence of prompt diagnosis and treatment, it rapidly progresses to tractional retinal detachment (stage 4 or 5 ROP) and can cause blindness.[1,2] In developing countries like India, it is has been reported in larger infants, as well.[3,4] In infants with type 1 early treatment for retinopathy of prematurity (ETROP), treatment with near confluent laser therapy has been regarded as a standard of care,[5,6] however its outcomes in APROP are poor, with unfavorable structural outcomes ranging from 14.3% to 28.6%.[6-8] Laser ablation induces long-term sequalae suh as the limited field of vision and higher myopia.[9] On the other hand, intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) results in prompt resolution of plus disease with regression of ROP, with the potential for further retinal vascular development. This may reduce the need for ablation of the peripheral avascular retina, decreased treatment time with less stress for the neonate and induce less myopia.[10-12] Unfavorable structural outcomes and late recurrence of disease and thus need for longer follow-up are common issues with anti-VEGF monotherapy[10,13-15] To overcome the disadvantages of conventional laser as well as anti-VEGF monotherapy, combined treatment has been evaluated in infants with Zones I and II ROP, which showed promising anatomical outcomes.[12] Similarly, outcomes of rescue laser after initial treatment with anti-VEGF therapy had also shown good results in APROP.[16]

In adults, Bevacizumab has a longer half-life and it takes ≥2 months for its clearance from the systemic circulation, whereas Ranibizumab has a modest effect on plasma VEGF levels, Which tends to return to baseline within 1 week of treatment.[17,18] Carneiro *et al*. reported that Ranibizumab did not alter systemic VEGF concentrations in adults.[19] A significantly higher chance of high myopia has also been reported with Bevacizumab.[20] Thus, Ranibizumab may be a safer and preferred anti-VEGF in infants with ROP.

After an injection of anti-VEGF, peripheral retinal vascularization tends to increase over several months.[11,12] As a result, if the laser can be deferred by an injection of anti-VEGF, a relatively smaller area of the peripheral avascular retina may need to be ablated, resulting in a fewer number of laser spots, less duration of laser with resultant more functional peripheral retina and less myopia. With this aim, we planned this prospective study in infants of APROP treated with

Consultant Vitreo Retina Services, Vitreoretina Services, [1]Director, [2]DNB Trainee, MGM Eye Institute, Raipur, Chhattisgarh, [3]Professor of Ophthalmology, Regional Institute of Ophthalmology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

Correspondence to: Dr. Anil Babanrao Gangwe, MGM Eye Institute, 5th Mile, Vidhan Sabha Road, Raipur, Chhattisgarh – 493 111, India. E-mail: anil@mgmeye.org

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intravitreal injection of Ranibizumab followed by laser at an early or deferred stage, to compare the structural outcomes, refractive error, and the procedure of laser between the groups.

Methods

A prospective, randomized, interventional study was designed and conducted from September 2017 to January 2019. Following approval from the institutional review board, we included all the infants diagnosed as APROP during ROP screening at multiple neonatal intensive care units (NICUs). Sample size was calculated by assuming the incidence of ROP in India as 40% (in infant <37 weeks of gestational age).[2] Among the infants with ROP, 16% have ROP which requires treatment and out of these, 13.1% are APROP.[21] A sample size of 30 infants (60 eyes) was calculated using a confidence limit of 5%, design effect of one and dropout rate of 10%. Human subjects included in the study were under the tenets of the Declaration of Helsinki. The screening was done as per the National Neonatology Forum (NNF) of India's guidelines,[2] and APROP was diagnosed as per the description of the International Classification of ROP (ICROP).[1] Though, ICROP does not subclassify zone 1 disease, we anatomically sub-classified zone 1 APROP in to anterior and posterior for subgroup analysis. Posterior zone 1 was defined as a circle centered on the optic nerve head with a diameter equivalent to the distance between center of disc and anatomical fovea. Part of zone one beyond this area was labeled as anterior zone 1.[22]

After obtaining parental consent, infants with APROP received 0.25 mg in 0.025 ml of intravitreal Ranibizumab (IVR),[15] injected using 30-gauge needle at 1.5 mm from the limbus under aseptic condition using topical anesthesia in both the eyes in single sitting in the main operation theatre. After IVR, infants were randomized into two groups alternately; odd numbers to group 1, the early laser group, and even numbers to group 2, the deferred laser group. The early laser was defined as laser done at 1 week after receiving IVR [Fig. 1a-c] while the deferred laser was defined as laser done at 6 weeks after receiving IVR or after a recurrence of plus disease whichever was earlier [Fig. 1d-f]. Six weeks was taken as the benchmark for deferred laser, as most cases of recurrence or reactivation after initial IVR tend to occur after 6 weeks.[13-15] The infants in group 2 were Followed up weekly to monitor the growth of retinal vessels and recurrence of plus disease or appearance of peripheral retinopathy. The laser was done using Diode laser indirect ophthalmoscope (Iridex® Germany) under topical anesthesia in NICU after obtaining written informed consent from the parents. Screening and treatment was performed by two of the authors. Fundus photographic documentation was done for all the infants at each session using a pediatric wide-field camera (RetCam Shuttle, Clarity Medical Systems, Inc. USA).

The primary objective of the study was to compare the structural outcomes (favorable or unfavorable) between infants undergoing laser at an early or deferred stage after receiving IVR. The favorable structural outcome was defined as complete regression of the disease, characterized by the disappearance of plus disease and peripheral retinopathy, six weeks after the laser. The unfavorable structural outcome was defined as the presence of active disease, characterized by persistence or recurrence of plus disease with or without recurrence of peripheral retinopathy in the absence of any unlasered areas, at six weeks after the laser. Progression to tractional retinal detachment, significant pre-retinal hemorrhage obscuring macula, regression with cicatricial sequalae like the development of falciform retinal fold or shortening of the major arcade vessels or temporal dragging of fovea were also categorized as unfavorable structural outcomes. Other

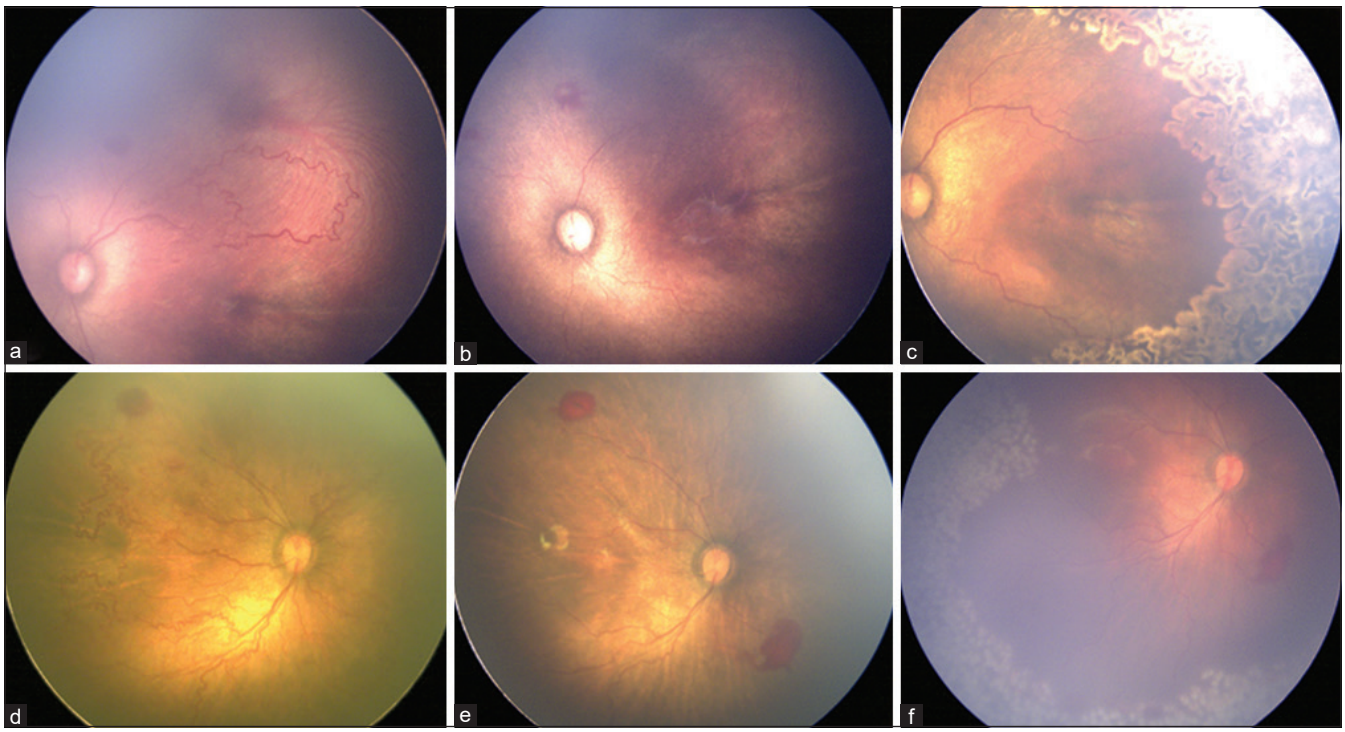

Figure 1: Clinical photographs (a-c) Early laser group; (d-f) Deferred laser group) (a) Zone 1 Aggressive posterior retinopathy of prematurity (APROP) before treatment (b) Regression of plus disease in Zone 1 APROP after Intravitreal Ranibizumab (IVR) (c) Regression of retinopathy and plus disease after laser (1 week after IVR) (d)Zone 1 APROP before treatment (e) Regression of plus disease in Zone 1 APROP after IVR (f) Fundus photograph immediately after laser (6 weeks after IVR)

outcome measures included, number of laser spots, duration of laser procedure and refractive error measured as spherical equivalent (SE) at 6 months follow-up.

Descriptive statistics like measures of central tendency (mean, median and frequency distribution) and measures of dispersion (standard deviation) were used to describe the data. To compare favorable and unfavorable outcomes between 2 groups, the Mann-Whitney U test was used. To measure refractive error, the number of spots of laser and duration of laser in two groups, we performed an independent sample T-test. All the tests were performed using statistical software SPSS16.0. A value of $P < 0.05$ was considered statistically significant.

Results

During the study period, a total of 793 eligible infants were screened for ROP. Among those screened, 429 (54.1%) infants had ROP and 101 (12.7%) infants required treatment. Among the infants who required treatment, 33 (32.7%) had APROP. The assignment of the study population is shown in [Fig. 2]. Sixty-three eyes of 32 infants having APROP, with mean gestational age (GA) of 30.2 ± 2.3 weeks and mean BW of 1294 ± 373 grams were included in the study. After receiving IVR, 16 infants were randomized in each group. Both the groups were comparable in terms of baseline characteristics, clinical features and disease severity [Table 1]. There was no ocular adverse event related to IVR in either of the groups. One infant in group 2 had congenital nasolacrimal duct obstruction in the left eye. The right eye received IVR and was included in the study. Left eye was treated with laser monotherapy and regressed without any additional treatment.

Among the infants included in the study, 12 (24 eyes, 75%) infants in group 1 and 11 (22 eyes, 68.7) infants in group 2 had zone 1 APROP and more than half of these were zone 1 posterior APROP (Group 1:16 eyes of 8 infants; Group 2: 14 eyes

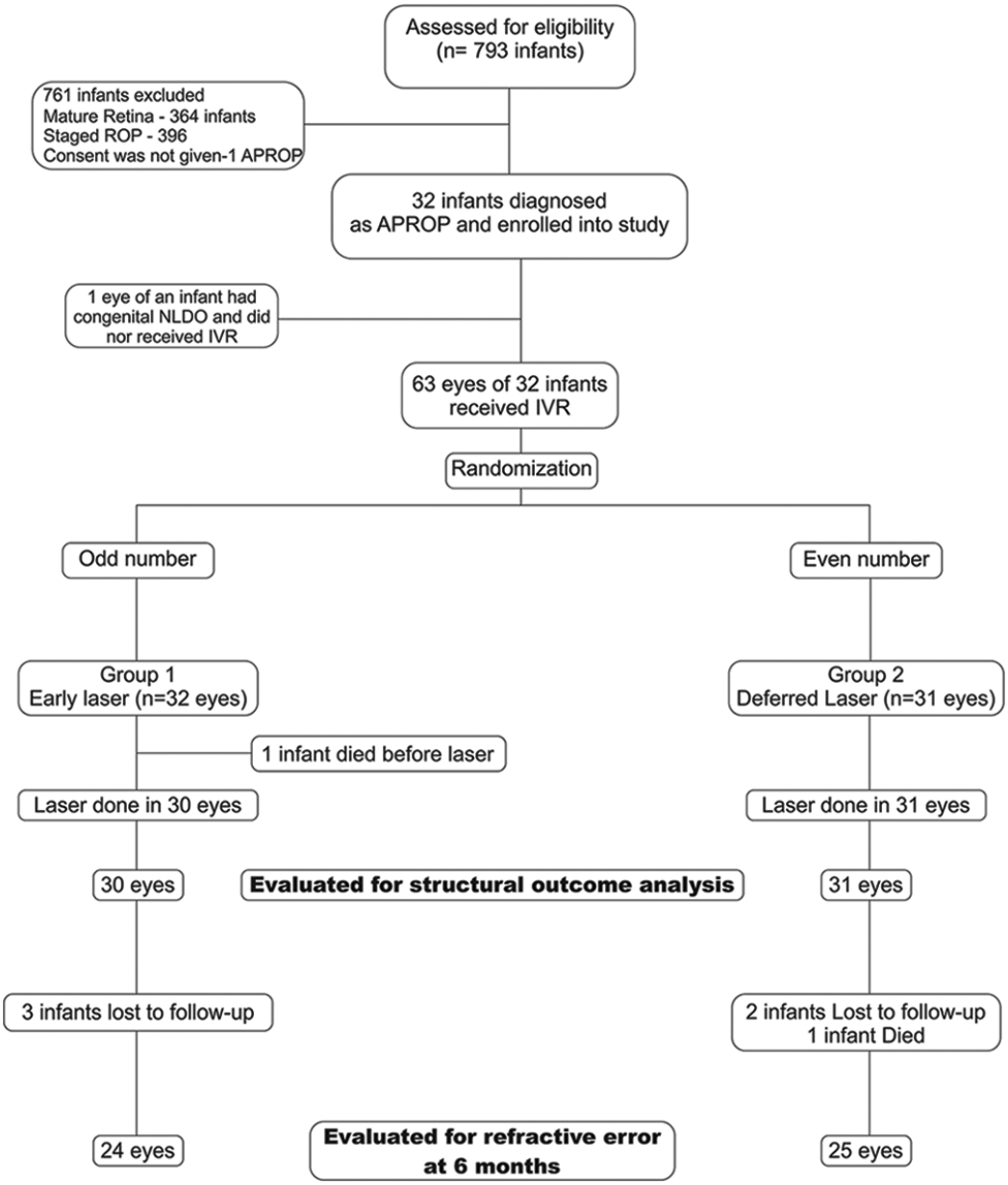

Figure 2: Assignment of study population

Table 1: Demographic profile and clinical features

Demographic details	Group 1 (%)	Group 2 (%)	*P*
Number of infants	16	16	
Gender			
Male	8 (50)	6 (37.5)	0.72
Female	8 (50)	10 (62.5)	
Mean GA±SD (weeks)	30.3±2.3	30.2±1.4	0.88
Mean BW±SD (grams)	1401.2±441.9	1187.2±244.4	0.11
Mean PMA at first visit±SD (weeks)	33.6±2.2	33.9±2.3	0.70
Clinical features			
No. of eyes	32	32	-
Dilatation of pupil			
Good	20 (62.5)	16 (50)	0.61
Poor	12 (37.5)	16 (50)	
NVI			
Present	12 (37.5)	16 (50)	1.00
Absent	20 (62.5)	16 (50)	
Tunica vasculosa lentis			
Present	16 (50)	20 (62.5)	0.31
Absent	16 (50)	12 (37.5)	
Vitreous haze			
Present	8 (25)	12 (43.7)	0.58
Absent	24 (75)	20 (62.5)	
Zone of APROP			
Zone 1			
Posterior	16 (50)	14 (43.8)	0.83
Anterior	8 (25)	8 (25)	
Zone 2	8 (25)	10 (31.2)	

GA - Gestational age, SD - Standard deviation, BW - Birth weight, PMA - Post menstrual age, NVI - Neovascularization of iris, APROP - Aggressive posterior retinopathy of prematurity

of 7 infants, $P = 0.83$). In group 2, 14 (45.1%) eyes of 7 infants, including 6 eyes with zone 1 posterior APROP, required laser before six weeks after IVR, due to recurrence of plus disease. The mean time for recurrence after IVR was 3.57 ± 0.97 weeks. In group 2, the GA, BW, and location of disease for infants who had recurrence of plus disease before 6 weeks, was comparable to those who did not had recurrence before 6 weeks [Table 2]. A favorable structural outcome was seen in 27 (90%) and 29 (93.5%) eyes in groups 1 and 2 respectively, but did not achieve statistical significance ($P = 0.61$). Unfavorable structural outcomes were seen in 3 (10%) eyes of 2 infants in group 1 and both (6.4%) eyes of an infant in group 2. In group 1, one infant had recurrence of plus disease in both eyes after laser and another had vitreous hemorrhage (VH) obscuring foveal center. In group 2, an infant had recurrence of plus disease after laser in one eye and other eye progressed to TRD. Eyes with recurrence of plus disease after complete laser were treated with repeat IVR injection while eyes with VH and TRD were referred for lens sparing vitrectomy (LSV). Eyes with recurrence of plus disease regressed after repeat IVR. Infant with VH had clear posterior pole with attached retina following LSV, while infant with TRD in one eye was lost follow-up, after receiving repeat IVR in other eye. All 5 eyes with unfavorable structural had zone1 posterior ROP at initial diagnosis. All 18 eyes with zone 2 APROP (8 eyes in Group 1 and 10 eyes in group 2) had favorable structural outcome. The mean number of laser spots required per eye in group 1 (2570.8 ± 615) was more than for group 2 (2149.8 ± 688.7) ($P = 0.01$). The mean duration of laser per eye was 46.8 ± 14.1 min for group 1 and 40.5 ± 14.7 minutes for group 2 At six months after laser eyes in group 1 (mean SE –1.0 ± 1.3 D) had more myopic refractive shift those in group 2 (mean SE + 0.5 ± 1.9D) ($P = 0.02$) [Table 3].

Discussion

In this study, we observed 59 eyes (96.7%) of infants with APROP treated with a combination of IVR and an early or deferred laser had a favorable structural outcome. Both the groups had comparable structural outcomes. However, the

Table 2: Group 2 subgroup analysis

	Laser at 6 weeks	Laser <6 weeks	*P*
Number of infants	9	7	
Number of eyes	17	14	
Mean GA±SD (weeks)	31±2.55	29.14±2.19	0.335
Mean BW±SD (grams)	1242.78±193.25	1115.71±314.41	0.147
Zone 1 APROP			
Anterior	3	4	
Posterior	8	6	
Total	11	10	
Zone 2 APROP	6	4	
Recurrence in weeks	NA	3.57±0.97	
Mean no. of spots per eye±SD	1850.06±771.16	2513.71±320.18	0.005
Mean duration of laser+SD (mins)	11.82±5.51	15.64±3.27	0.030
Structural outcome			
Favorable	17	12	0.113
unfavorable	0	2	
Refractive error at 6 months			
No. of eyes	15	10	
Spherical equivalent±SD (Diopter)	0.94±0.95	-0.05±2.90	0.223

GA - Gestational age, SD - Standard deviation, BW - Birth weight, APROP - Aggressive posterior retinopathy of prematurity

Table 3: Treatment and outcomes

	Group 1 (%)	Group 2 (%)	*P*
No. of eyes receiving IVR	32	31	-
Laser parameter			
No. of eyes treated	30	31	-
Mean no. of spots per eye±SD	2570.8±615	2149.8±688.7	0.01
Mean duration of laser±SD (mins)	46.8±14.1	40.5±14.7	0.09
Structural outcomes			
Favorable	27 (90)	29 (93.5)	0.61
Unfavorable			
Recurrence of plus disease after laser	2 (6.7)	1 (3.2)	-
Progression to TRD	0	1 (3.2)	
Vitreous hemorrhage	1 (3.3)	0	
Total	3 (10)	2 (6.4)	
Refractive error at 6 months			
No. of eyes	24 (80)	25 (80.6)	-
Spherical equivalent±SD (Diopter)	-1.0±1.3	+0.5±1.9	0.002

IVR - Intravitreal Ranibizumab, SD - Standard deviation, TRD - Tractional retinal detachment

deferred laser group needed significantly fewer laser spots and had less myopia at 6 months after laser. To the best of our knowledge, this is the first study wherein a large cohort of relatively larger Indian infants with APROP has been treated with a combination of IVR and an early or deferred laser with better structural outcomes than laser monotherapy.[6,8]

Favorable structural outcomes

To the best of our knowledge, there is no report comparing outcomes of laser monotherapy or combination therapy using Ranibizumab in infants with APROP. Yoon *et al.*, had compared outcomes of laser monotherapy with a combination of intravitreal Bevacizumab (IVB) followed by either zone 1 sparing or deferred laser in type 1 zone 1 ROP. They reported 100% favorable structural outcomes in eyes treated with combined IVB and laser.[12] In our study, 59 (96.7%) eyes had favorable structural outcomes at final follow-up. The possible reasons for marginally less favorable structural outcome in the current study may be the specific inclusion of eyes with APROP, a large proportion of eyes with zone 1 posterior APROP in each group as well as the use of IVR. Overall treatment outcomes in APROP have been reported to be worse than staged ROP, while recurrence of retinopathy or plus disease has been more common and earlier with the use of Ranibizumab than Bevacizumab.[8,15,22,23] Nevertheless we believe, 96.7% favorable outcome in eyes with APROP has not been previously reported. Yoon *et al.* reported a better anatomical outcome with combined IVB and zone 1 sparing or deferred laser than conventional laser monotherapy. However, there was no difference in anatomical outcomes between IVB with concomitant laser or deferred laser.[12] In this study also, there was no statistically significant difference in the structural outcome after early or deferred laser at 6 weeks after laser. The structural outcome of Zone 2 disease was better than those with Zone 1 disease, which has been reported previously.[13,22]

Unfavorable structural outcomes and zone 1 posterior APROP

All eyes with unfavorable structural outcome had zone 1 posterior APROP at initial diagnosis. Structural outcomes of conventional laser monotherapy for zone 1 APROP are poor with more than 50% of eye progressing to stage 5 even after adequate laser.[24] This study had 30 eyes with zone 1 posterior APROP at final analysis and 25 eyes (83.3%) achieved favorable outcomes after combined IVR and laser therapy. Findings from our study substantiate that, combination therapy for eyes with zone 1 posterior APROP has better structural outcomes than laser monotherapy.[24]

Laser procedure

Deferred laser after IVR in group 2 possibly provided more time for the vascularization of the peripheral retina. This could have reduced the total area of avascular retina to be ablated. However, the time taken to perform laser in both groups was not statistically different. This may be explained by the fact that the procedure of laser is dependent upon the extent of the avascular retina as well as the infant's systemic status at the time of the procedure. Technical difficulties in the laser of larger infants after IVR may prolong the total duration for the laser procedure.

Refractive error

At 6 months after laser, the early laser group showed more myopia as compared to the deferred laser group (–1.0 D and +0.5 D). However, a follow up of 6 months is relatively short to conclusively comment on the status of refractive error after laser for ROP. Yoon *et al.* also reported a more myopia in the infants treated with IVB and zone 1 sparing laser (–5.53 ± 2.21 D) than those treated with IVB and deferred laser (-1.40 ± 2.19 D) at a mean of 60 weeks of chronological age.[12]

In this study, 14 (45.1%) eyes in group 2 had a recurrence of plus disease within six weeks of IVR. This is much earlier than reported in the literature. In this study, however, we had not documented the effect of other possible contributory factors like anemia, thrombocytopenia, and postnatal weight gain which can possibly affect the recurrence of disease as well as response to treatment.[25] Some of the limitations of this study are, relatively small sample size and short follow-up for refractive error. We did not perform fundus fluorescein angiography after IVR, which could have given better judgment about the extent of retinal vascularization particularly in group 2. For an infant who died following IVR, we were not able to ascertain the possible cause of death or its relationship with the use of Ranibizumab.

Conclusion

We conclude that infants with APROP treated with a combination of IVR and laser have favorable structural

outcomes. Furthermore, both early, as well as deferred laser after IVR have comparable structural outcomes in APROP. Moreover, eyes undergoing deferred laser require a fewer number of laser spots and have less myopia at 6 months after laser. However, eyes planned for the deferred laser after IVR warrants a vigilant follow up for early identification and treatment of recurrence.

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Conflicts of interest

There are no conflicts of interest.

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