Original Article

Variation in the vitreoretinal configuration of Stage 4 retinopathy of prematurity in photocoagulated and treatment naive eyes undergoing vitrectomy

Salil Sharad Gadkari, Madan Deshpande

Purpose: We sought to document the difference in the vitreoretinal configuration of Stage 4 retinopathy of prematurity (ROP) in photocoagulated and treatment naive eyes undergoing vitrectomy and to correlate it with surgical complexity. **Methods:** Consecutive eyes posted for vitrectomy with Stage 4 ROP were documented preoperatively using a RetCam for the presence of peripheral traction (PT), presence of central traction just outside the arcades, and presence of traction extending to the lens. A note was made of the following intraoperative events: lensectomy, intraoperative bleeding, and iatrogenic breaks. Wilcoxon rank-sum test was used for analysis. **Results:** From a total of 46 eyes, 16 and 30 eyes were from the treated and treatment naive group, respectively. More eyes in the treated group had central ($P < 0.0001$) and lenticular traction ($P = 0.022$). More eyes in the untreated group had PT ($P < 0.0001$). A significant number of eyes without photocoagulation needed lensectomy ($P = 0.042$), and no difference in intraoperative bleeding ($P = 0.94$) was demonstrable. Iatrogenic retinotomy occurred in three eyes, all naive. Notably, age at surgery was more in the untreated group ($P = 0.00008$). **Conclusion:** Vasoproliferative activity in all retinopathies occurs at the junction of the ischemic and nonischemic retina. In the natural course of ROP, this takes place peripherally, at the ridge. In photocoagulated eyes, this junction is displaced posteriorly due to peripheral ablation. Treated eyes manifested with posterior proliferative changes and were more amenable to lens-sparing vitrectomy. Naive eyes were older when they underwent surgery to relieve PT with greater chances of lensectomy and iatrogenic breaks.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1_17

Quick Response Code:

Key words: Retinopathy of prematurity surgery, retinopathy of prematurity surgical anatomy, retinopathy of prematurity vitrectomy, Stage 4 retinopathy of prematurity

Unlike in developed countries with adequate retinopathy of prematurity (ROP) screening and treatment facilities, we encounter patients with Stage 4 ROP requiring surgery, from two groups. Some have progressed despite prior laser treatment and a significant percentage that are treatment naive. Vasoproliferative activity in all retinopathies occurs at the junction of the ischemic and nonischemic retina. In the natural course of ROP (untreated eyes), this takes place peripherally, at the ridge.[1] In photocoagulated eyes, this junction is displaced posteriorly due to peripheral ablation. We sought to document the difference in the vitreoretinal configuration in these two groups and to correlate it with surgical complexity.

Methods

This prospective cohort study was conducted after obtaining Ethics Committee approval. The presence or absence of laser prior to presentation constituted the "exposure" in this cohort. Consecutive eyes posted for vitrectomy with Stage 4 ROP between March 2013 and May 2015 were documented 1 day preoperatively using a RetCam (Clarity Medical Systems, Inc., Pleasanton, CA).[2] A careful assessment of traction forces was done. These were defined as peripheral traction (PT), central traction (CT), and traction to the lens. CT was defined as traction extending from the ridge which was typically just outside the vascular arcades, always posterior to the equator and extended toward the ora and/or optic disc. Lens traction was traction extending from the ridge toward the lens (anterior hyaloid). Traction was defined as PT when it extended from the ridge in the periphery to the ora serrata. The extent of PT could be expressed in clock hours and could be adherent to the peripheral lens capsule. These findings were corroborated by a blinded photo reviewer.

A three-port pars plana vitrectomy was performed for all the patients.[3-6] The surgical plan was always to perform a lens-sparing vitrectomy. The decision to perform a lensectomy was taken in those cases where it was not possible to release the traction using lens-sparing vitrectomy. These eyes usually had more than 6 clock hours of PT and/or adherence of the peripheral retina to the lens capsule. Vitrectomy was performed using the Alcon Constellation vitrectomy platform (Alcon

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Manuscript received: 01.01.17; Revision accepted: 17.05.17

Cite this article as: Gadkari SS, Deshpande M. Variation in the vitreoretinal configuration of Stage 4 retinopathy of prematurity in photocoagulated and treatment naive eyes undergoing vitrectomy. Indian J Ophthalmol 2017;65:846-52.

laboratories, Fort worth, TX, USA). All patients were operated with the 25-gauge systems. The sclerotomy was made 1½ mm posterior to limbus and its location was modified depending on peripheral retinal traction. The trocar cannula system was used to increase the safety and ease of instrument insertion. A few modifications were made as follows. The trocar cannula was inserted half way; the trocar withdrawn prior to the cannula being pushed in completely to prevent damage to the elevated retinal tissue in a smaller globe. The valved cannula system was preferred as the chances of intraocular pressure drop during insertion-removal of instruments, resulting in bleeding, were minimized. All the dissections of vitreous membranes were done by the cutter due to excellent control and the port being closer to tip. Fluid–air exchange was performed at the end of the procedure. All sclerotomies were sutured with 8-0 vicryl to ensure adequate closure of the neonatal sclera.

The various vitreoretinal tractions documented preoperatively were confirmed during vitrectomy. A note was made of the following intraoperative events: lensectomy, intraoperative bleeding, and iatrogenic breaks. Wilcoxon rank-sum test was used, due to the small data size, to analyze the differences in the vitreoretinal configuration between the treated and treatment naive groups.

Results

The study group had 46 eyes with Stage 4 ROP who underwent surgery. A total of 16 and 30 eyes were from the treated and treatment naive groups, respectively [Table 1]. Intraobserver variation used to ascertain correlation between the preoperative RetCam images and the intraoperative visualization of the vitreoretinal configuration by the same observer had a kappa value of 1.

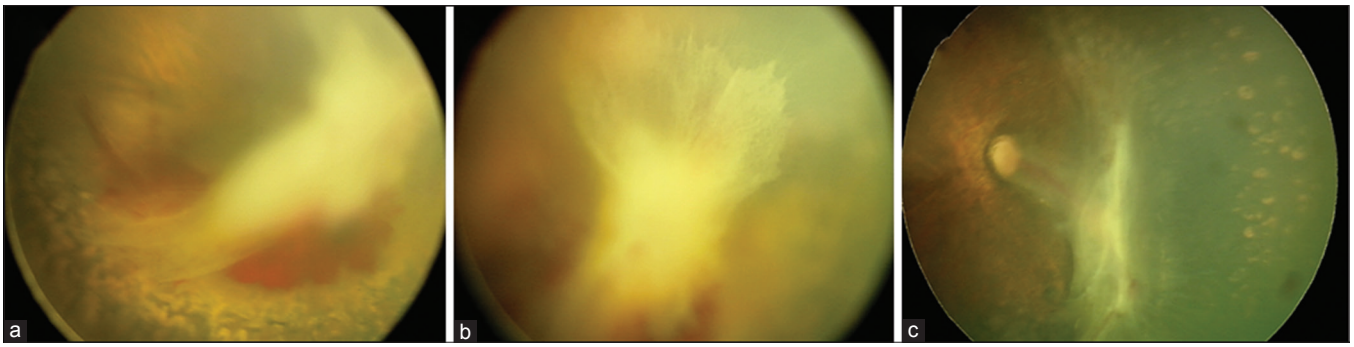

Figure 1: Gestational age 32 weeks, birth weight 1600 g. Progressed despite laser. RetCam picture (a) central traction, (b) lens traction, (c) after vitrectomy

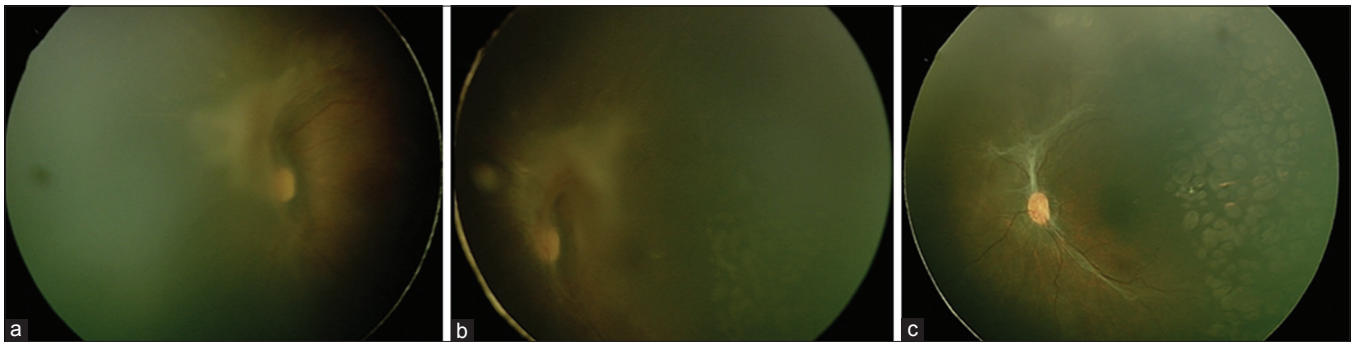

Figure 2: Gestational age 28 weeks, birth weight 1800 g. Progressed despite laser. RetCam picture (a and b) central traction and lens traction extending into the vitreous, respectively, (c) after vitrectomy – left eye

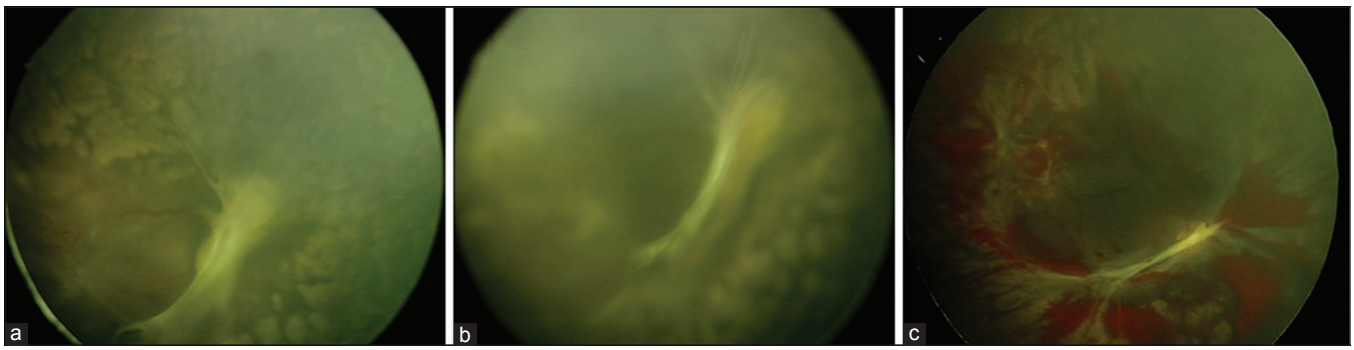

Figure 3: Gestational age 32 weeks, birth weight 1450 g. Progressed despite laser. RetCam picture (a and b) central traction and lens traction extending into the vitreous, respectively, (c) after vitrectomy – left eye

There were a higher number of children with CT in the treated compared to the untreated group ($P < 0.0001$) with a distribution of 76.2% of eyes in the treated as compared to 23.8% in the untreated group [Figs. 1-5]. There were a greater number of children with lenticular traction in the treated compared to the untreated group ($P = 0.022$), with a distribution of 63.6% of eyes in treated group as compared to 36.4% in untreated group. However, there were a higher number of children with PT in the untreated compared to the treated group ($P < 0.0001$), with a distribution of 88.2% of eyes in the untreated group as compared to 11.76% of eyes in the treated group [Figs. 6-9].

One-third of eyes without photocoagulation needed lensectomy ($P = 0.042$) as compared to a single eye in the lasered group. About 2/16 eyes in the lasered group and 4/20 in the naive group had intraoperative bleeding, which was not statistically significant ($P = 0.94$). Iatrogenic retinotomy occurred in three eyes, all treatment naive. Notably, the postmenstrual age (PMA) at surgery of children in the treated group was less, 40.8 weeks (standard deviation [SD] =1.79), while in the untreated group, it was 49.3 weeks (SD = 8.5) ($P = 0.00008$).

Discussion

The genesis of all retinopathies is retinal ischemia. Further course of the disease pivots around the response to this insult and manifests in the form of development of new vessels from the nonischemic retinal tissue. Neovascularization occurs at the junction of the ischemic and nonischemic tissue.[7]

ROP is characterized by retinal ischemia in the far periphery of the retina where the immature retinal vasculature has still to reach and its completion is interrupted by premature birth and subsequent insults.[8] The natural course of the disease consists of the development of a ridge of neovascular tissue at the boundary of the ischemic areas. This may be followed by the development of traction bands with subsequent varying degrees of traction retinal detachment.[9] The development of these traction bands in the neonatal vitreous is different from that in adults. Proliferative changes can occur along the Cloquet canal or along the anterior hyaloid, rarely seen in adult eyes.[10]

The traction forces described in ROP are ridge to ridge, traction extending to the retro-lental area, anterior traction from the ridge to the ora serrata, and traction extending from the ridge to the disc posteriorly.[9] We did document these traction forces by B-scan ultrasonography using a 12 MHz probe and ultrasound biomicroscopy. However, we felt it was suffice to rely on RetCam pictures taken to focus on the posterior, mid, and anterior vitreous to clearly document the vitreoretinal relations as the study eyes had clear media. Further, these findings were confirmed during vitreous surgery.

The profile of patients coming to us for ROP surgery either picked through our screening service or directly due to referral differed from those seen in more developed countries. The children seen were heavier, older, and unablated, reflecting the inadequacy of the neonatal care and screening services available. Hence, patients coming to us with Stage 4 ROP had larger numbers of those who were untreated as compared to the treated ones.[11]

In our opinion, the vitreoretinal configuration of the two groups differed because of the difference in the location of the proliferative activity. The PT and CT stated are variants of the ridge to ora traction – but defined differently – in this study, by the location of the ridge. The ischemic areas in the untreated group were located more peripherally except in exceptional cases. This resulted in proliferation taking place more peripherally. In this location, the PT from the ridge to the ora becomes the dominant feature [Fig. 10]. PT is surgically most difficult to address. This requires meticulous dissection

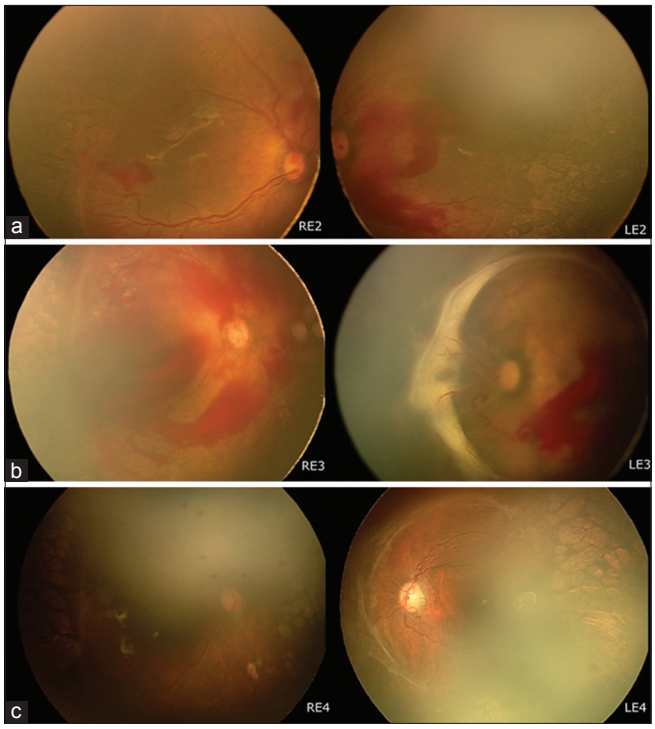

Figure 4: Gestational age 32 weeks, birth weight 700 g. Progressed despite laser. RetCam picture (a) both eyes postlaser, (b) both eyes after progression (note central traction), (c) both eyes after vitrectomy (courtesy MEAJO)

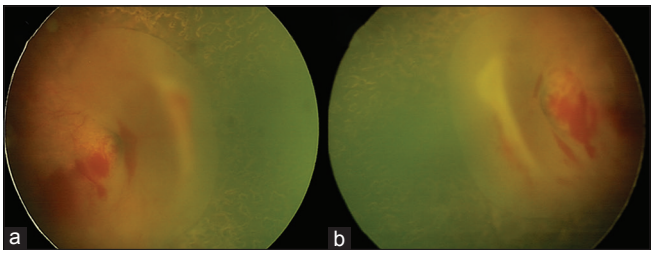

Figure 5: Gestational age 28 weeks, birth weight 1400 g. Progressed despite laser. RetCam picture (a and b) central traction in the right and left eyes, respectively. Note the proliferation at the edge of lasered area

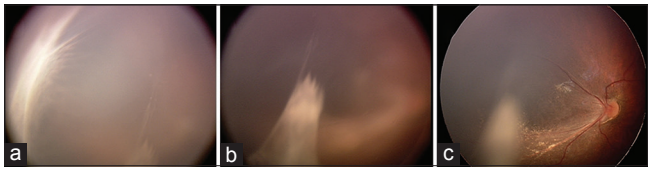

Figure 6: Gestational age 30 weeks, birth weight 1444 g. Treatment naive. RetCam picture (a) anteriorly focused picture showing peripheral traction, (b) lens traction, (c) posterior pole

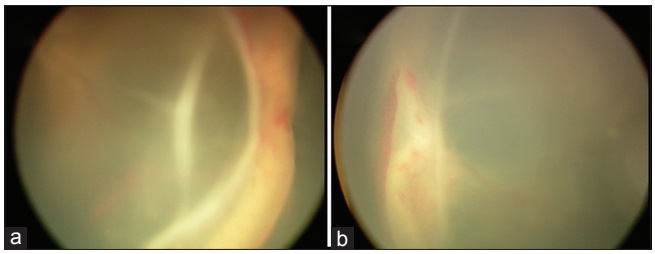

Figure 7: Gestational age 28 weeks, birth weight 914 g. Treatment naive. Anteriorly focused picture showing peripheral traction. RetCam picture (a) right eye, (b) left eye

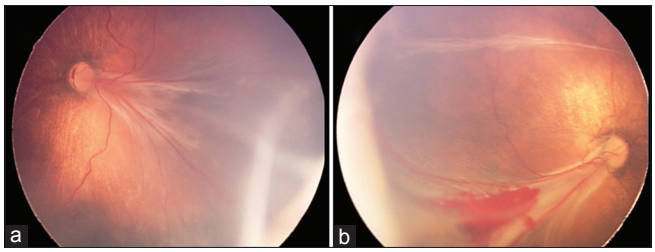

Figure 8: Gestational age 30 weeks, birth weight 1170 g. Treatment naive. Presence of peripheral traction causing folds. RetCam picture (a) right eye, (b) left eye

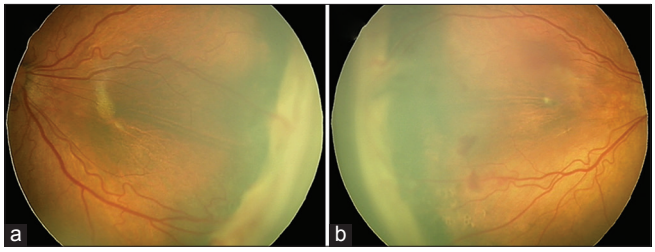

Figure 9: Gestational age 31 weeks, birth weight 1140 g. Treatment naive. Picture showing the peripheral traction. RetCam picture (a) right eye, (b) left eye

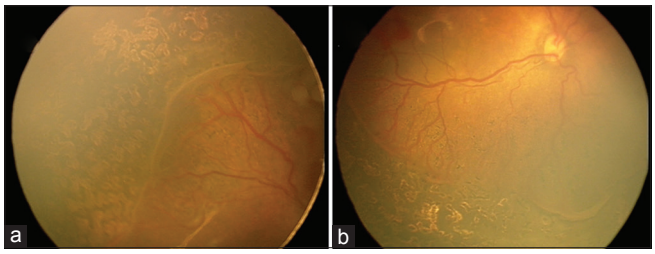

Figure 11: (a and b) RetCam picture highlighting the presence of the ridge just outside arcades and at the junction of the lasered and nonlasered area. The few laser marks seen posterior to the ridge were a failed attempt at trying to arrest the disease after progression which was noted despite adequate laser

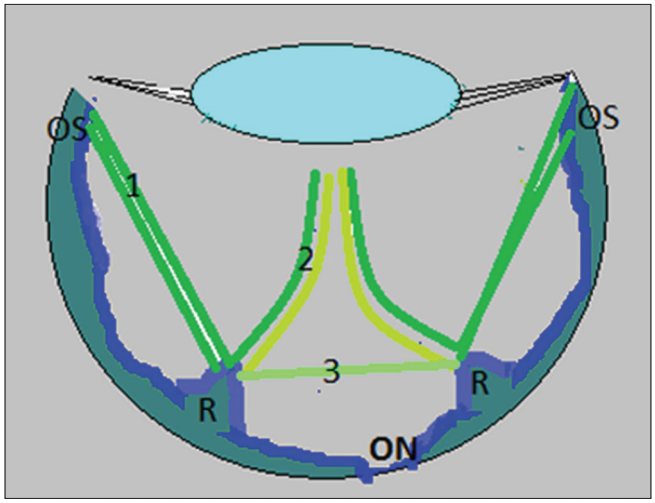

Figure 10: Schematic diagram showing vitreoretinal traction in treatment naive eyes. ON: Optic nerve head, OS: Ora serrata, R: Ridge, 1: Peripheral traction (peripheral ridge to ora), 2: Lens traction, 3: Ridge-to-ridge traction, 4: Ridge-to-optic nerve traction

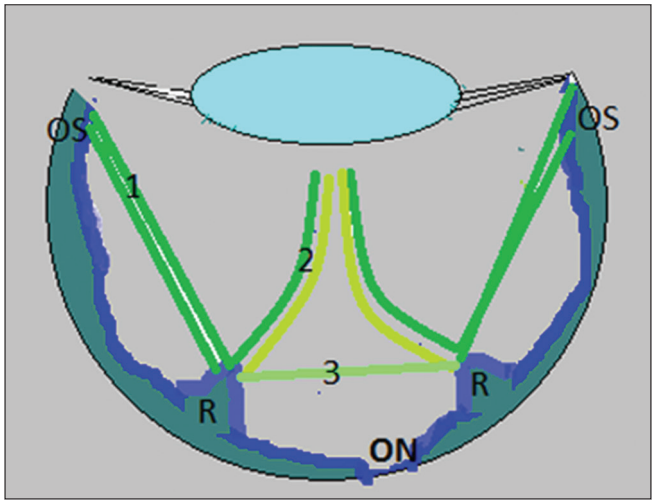

Figure 12: Vitreoretinal traction in laser-treated eyes. ON: Optic nerve head, OS: Ora serrata, R: Ridge, 1: Central traction (posterior ridge to ora), 2: Lens traction, 3: Ridge-to-ridge traction

with indentation. The chances of inadvertent iatrogenic breaks are higher in this group. With progression, the membrane contacts and the ridge are pulled closer to the ora, making dissection even more difficult. All three iatrogenic breaks occurred in this group. The gradual creeping of fibrovascular tissue over the peripheral lens also results in much higher chances of lensectomy to gain surgical access. The peripheral ridge encompassing more clock hours was likely to progress to a retro-lental membrane (not a subject of this study) from ridge-to-ridge traction.[12]

Normally in an untreated eye with ROP, the ischemic retina is located anteriorly-distally-peripherally and the nonischemic retina posteriorly-proximally-centrally, depending on the terminology used. In patients who have had adequate laser, sometimes up to the arcades and have not stabilized, proliferation as expected takes place at the junction of ischemic and nonischemic retina [Fig. 11]. However, paradoxically, the ablated nonischemic retina is peripheral and the ischemic retina is central. In this clinical scenario, more laser is not possible as adequate laser has already been done up to arcades [Fig. 4].[13]

Further treatment of already adequately treated peripheral retina is unlikely to favorably affect the outcome in these cases and can in fact increase the chances of its adverse effects. The progression is fueled by ischemic tissue at the posterior pole

Table 1: List of eyes in the study with information about the gestational age in weeks, birth weight (g), postmenstrual age (weeks) at surgery, interval between retinal laser and surgery in days, anti-vascular endothelial growth factor use, presence or absence of prior laser treatment, peripheral traction, central traction, lens traction, lensectomy, intraoperative bleed, and iatrogenic retinotomy

GA (weeks)	BW (g)	PMA at surgery (week)	Laser-surgery interval (days)	Anti VEGF	Subgroup	Peripheral traction	Central traction	Lens traction	Lensectomy	Intraoperative bleed	Iatrogenic retinotomy
28	900	40	29		Treated	-	+	-	-	-	-
32	1600	39	32		Treated	-	+	-	-	-	-
31	1140	38	30		Treated	-	+	-	-	-	-
30	1444	57			Naive	+	-	-	-	-	-
28	950	40			Naive	+	-	+	+	-	-
31	1100	41			Naive	+	-	+	-	-	-
32	1300	39	14		Treated	-	+	-	-	-	-
30	1444	58			Naive	+	-	-	-	-	-
28	950	47			Naive	+	-	-	-	-	-
28	900	40	28		Treated	+	+	-	-	-	-
29	1000	42	15		Treated	-	+	-	-	-	-
30	1150	43			Naive	+	-	-	+	-	-
30	1170	58			Naive	+	-	-	+	+	-
26	700	44	35	Given	Treated	-	+	+	-	-	-
26	750	40	21		Treated	-	+	-	-	-	-
30	1170	59			Naive	+	+	-	-	-	-
30	1500	50			Naive	+	-	-	+	-	-
26	700	41	25	Given	Treated	-	+	-	-	-	-
28	1400	62			Naive	+	-	-	+	+	+
28	950	39	18		Treated	+	+	+	+	-	-
28	1400	64			Naive	+	-	-	-	-	-
27	750	44	15		Treated	-	+	+	-	+	-
30	1100	42	13		Treated	-	+	+	-	+	-
28	914	64			Naive	+	-	-	-	-	-
32	1600	41	18		Treated	-	+	+	-	-	-
30	1444	40	24		Treated	-	+	+	-	-	-
29	1200	36			Naive	+	-	-	+	-	-
28	914	65			Naive	+	-	-	-	-	-
27	900	41	30		Treated	-	+	+	-	-	-
27	950	43			Naive	+	-	-	-	-	-
30	1600	42			Naive	+	-	+	-	-	-
29	970	48			Naive	+	-	-	-	-	-
28	900	43	23		Treated	-	+	-	-	-	-
26	1800	44			Naive	+	-	-	-	-	-
31	1850	45			Naive	+	-	+	-	-	-
30	1700	47			Naive	+	-	-	-	-	-
28	920	47			Naive	+	-	-	+	-	-
29	1000	49			Naive	+	-	-	-	-	-
28	900	49			Naive	+	-	-	-	-	-
29	980	62			Naive	+	-	-	+	-	-
29	1000	41			Naive	+	-	-	+	-	-
31	1800	39			Naive	+	-	-	+	-	+
30	1600	59			Naive	+	-	-	-	+	+
26	800	42			Naive	+	-	-	-	-	-
30	1600	43			Naive	+	-	-	-	-	-
31	1700	48			Naive	+	+	-	-	-	-

GA: Gestational age, BW: Birth weight, PMA: Postmenstrual age, VEGF: Vascular endothelial growth factor, +: Present, -: Absent

along with residual levels of vascular endothelial growth factor (VEGF) present till the laser ablation takes full effect. This is a specific indication for use of intravitreal anti-VEGF. This is significant, as blanket use of anti-VEGF in ROP is increasingly discouraged due to prolonged systemic VEGF suppression.[14,15] In this scenario, anti-VEGF therapy may be required till a PMA of 40 weeks, when downregulation of VEGF occurs.[16,17]

In treated eyes, the resulting vitreoretinal traction extends from this ridge (which is located posterior to the equator) to the ora peripherally. This traction often extends toward the posterior surface of the anterior hyaloids toward the crystalline lens [Fig. 12]. The proliferative activity toward the lens almost never occurs in conditions such as diabetic retinopathy. This presentation can be attributed to the remnants of the primary vitreous still present in the neonatal eye.[10]

In our series, the treated group eyes were more amenable to lens-sparing vitrectomy with fewer patients needing lensectomy. Dissection of posterior traction was a safer process with much lower chances of iatrogenic retinal breaks. Anterior traction toward the lens was effectively dealt by passing the cutter horizontally with the port sideways. There was no difference in encountering intraoperative bleeding in both the groups. The PMA at surgery and presence of thrombocytopenia can have an effect on intraoperative bleeding. Increasing infusion pressure, leaving behind air, and using valved cannula minimized the chances of bleeds.

The difference in the PMA at surgery, which was observed in our series, can be responsible for higher chances of bleeding at earlier age and increased fibrosis and therefore increased chances of iatrogenic retinotomy in older children. It can be concluded that children in the treated group had a more severe form of the disease that progressed despite retinal laser while the patients in the untreated group represented a milder form of the disease which would be easily preventable by timely screening and laser.

Complete correlation between pre- and intra-operative visualization of vitreoretinal configuration could face criticism for bias as both of these were reported by the same surgeon. The severity of ROP is known to be different in various races such as Caucasians, Hispanics, and Blacks.[18] Since our study group comprised Indians, the findings may not completely applicable to all races. In our practice settings, we often did not have a clear idea about the exact treatment given in the immediate postnatal period in the neonatal intensive care unit. All the patients in the untreated group were referrals from elsewhere, hence we were not in a position to opine on the zone of disease at presentation. Unfortunately, the two groups were not matched for PMA in our study and hence could not be used to draw conclusions about the differing risk of hemorrhage. It may appear that the manuscript is limited by a lack of context to other published literature. However, a 20-year systematic search in the following databases (Cochrane library, Medline, EM Base, Google advanced search, and Google scholar) and using the search terms "ROP Stage 4 after laser/without laser" did not show any study highlighting this variation.

Conclusion

Treated eyes had more posterior proliferative changes and were more amenable to lens-sparing vitrectomy. Treatment naive eyes needed relief of PT with greater chances of lensectomy and iatrogenic retinal breaks. Extension of proliferative activity toward the lens, which was noted, more commonly in the treated group, almost never occurs in other retinopathies. The paradoxical distribution of ischemic retina in eyes progressing despite laser photocoagulation was an interesting observation. Unfortunately, the two groups were not matched for PMA in our study and hence cannot be used to draw conclusions about the differing risk of hemorrhage.

Acknowledgments

The authors would like to thank Dr. Sucheta Kulkarni and Dr. Nilesh Kakade, consultant ophthalmologists, from the retinopathy of prematurity service, Mr. Umesh Pawar, optometrist for RetCam pictures, and Dr. PM Velankar, anesthesiologist, for their help in this study.

Financial support and sponsorship

This project was funded by a grant from Mr. Nitin Desai, Desai Brothers, Pune, Maharashtra, India.

Conflicts of interest

There are no conflicts of interest.

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