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

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Purpose: We sought to document the difference in the vitreoretinal configuration of Stage 4 retinopathy of prematurity (ROP) in photoacoagulated 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 photoacoagulation 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 photoacoagulated 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.

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. In photoacoagulated 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). 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. 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...
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.
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.
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...
| 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     |          |                   |                 |              |            |                   |                     |
| 29         | 950    | 47                    |                               | Naive     |          |                   |                 |              |            |                   |                     |
| 30         | 900    | 40                    | 28                            | Treated   |          |                   |                 |              |            |                   |                     |
| 29         | 1000   | 42                    | 15                            | Treated   |          |                   |                 |              |            |                   |                     |
| 30         | 1150   | 43                    |                               | Naive     |          |                   |                 |              |            |                   |                     |
| 30         | 1170   | 58                    |                               | Naive     |          |                   |                 |              |            |                   |                     |
| 29         | 1200   | 59                    |                               | Naive     |          |                   |                 |              |            |                   |                     |
| 30         | 1500   | 50                    |                               | Naive     |          |                   |                 |              |            |                   |                     |
| 26         | 700    | 44                    | 35                            | Given     |          |                   |                 |              |            |                   |                     |
| 26         | 750    | 40                    | 21                            | Treated   |          |                   |                 |              |            |                   |                     |
| 30         | 1170   | 59                    |                               | Naive     |          |                   |                 |              |            |                   |                     |
| 30         | 1500   | 50                    |                               | Naive     |          |                   |                 |              |            |                   |                     |
| 26         | 700    | 41                    | 25                            | Given     |          |                   |                 |              |            |                   |                     |
| 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.\textsuperscript{14,15} In this scenario, anti-VEGF therapy may be required till a PMA of 40 weeks, when downregulation of VEGF occurs.\textsuperscript{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.\textsuperscript{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. 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. 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.

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\textbf{Conflicts of interest}

There are no conflicts of interest.

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