Stage 5 retinopathy of prematurity: An update

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Abstract:

Retinopathy of prematurity (ROP) is one of the most common causes of preventable blindness in children. In spite of the availability of various treatment options, and favorable results with timely intervention, many infants present to the ophthalmologists in the advanced end stage of the disease due to lack of awareness especially in the developing nations. This blinding or Stage 5 of ROP presents with total retinal detachment and has to be managed surgically. The surgical techniques for Stage 5 ROP are unique and demanding. The successful anatomical results after surgery are only seen in 20%–50% of cases. In spite of a successful anatomical result, the visual outcome may be slow and limited. The use of newer pharmacological adjuncts has shown promising results. Because of heterogeneity of presentation of the disease severity, a genetic predisposition has also been proposed. A concerted effort from the pediatricians, ophthalmologists, and healthcare workers is required to establish effective screening and treatment guidelines to prevent blindness due to ROP. Till then surgical management has to be done. Parents must be educated regarding the limited visual benefits of surgery and the need for prolonged follow-up. This review gives a comprehensive overview of the pathogenesis, clinical aspects, surgical interventions, and their outcomes and future prospects of Stage 5 ROP.

Keywords:

Anatomical success, complications, functional success, retrolental fibroplasia, surgical management

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Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the premature infants characterized by abnormal vascularization at the junction of the vascular and avascular retina. If not diagnosed in time, it may result in significant visual impairment and in severe cases, such as Stage 5 ROP, it can lead to blindness-causing extreme distress to the children and their families. The first description of the disease was given in the 1940s when the end stage of ROP was termed as "retrolental fibroplasia."[1] Since then, two epidemics of ROP have been witnessed. The "first epidemic" in Europe and North America saw surge in cases of ROP due to the administration of excessive supplemental oxygen therapy.[2] Following

restriction in the usage of oxygen, there was a marked reduction in these epidemic proportions. With the advancement in neonatal care in the early 1970s, the survival rate of low-birth-weight (LBW) infants increased substantially resulting once again in resurgence in the number of ROP cases resulting in the second epidemic. The introduction of better neonatal intensive care units (NICUs) and availability of effective treatment in the form of cryotherapy and laser photocoagulation resulted in a decline in this "second epidemic" of ROP in developed countries. In developing countries, ROP still remains an important cause for blindness in children. Better survival rates of preterm babies and the lack of screening guidelines and effective healthcare program to regulate oxygen are now leading to a "third epidemic" in the middle- and lower-income countries in Latin America and Asia.[3] Reducing severe visual impairment in children in these countries

is one of the major targets of the global prevention of blindness initiative of the VISION 2020 the Right to Sight Program.[4]

Methods of Literature Search

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board. We performed a comprehensive literature search of all the articles related to Stage 5 ROP and published until May 2018 using PubMed and Google Scholar database. Maximum possible relevant articles related to this field were included to provide an overview of the pathogenesis, diagnosis, management, surgical outcomes, complications, and future prospects of the Stage 5 ROP. We have summarized the surgical techniques according to our experience as well to provide a wholesome picture of the current perspectives in Stage 5 ROP.

Classification of Retinopathy of Prematurity

The spectrum of the disease may vary from very mild cases that show spontaneous resolution to very severe cases that may cause complete bilateral blindness within the 1st year of life. In 1984, the extent of ROP was described in three zones, five stages, and the presence or absence of plus disease as per the International Classification of ROP.[5] The zones are described as three anterior-posterior zones as shown in Figure 1. Zone I is defined as a circle, centered on the disc, whose radius is twice the distance from the disc to the macula; Zone II extends from the edge of Zone I to the nasal ora serrata; and Zone III is the remaining temporal crescent of retina anterior to Zone II. As the disease evolves, five stages of increasing severity have been described. Stage 1 is that of a flat, white demarcation line present within the plane of the retina, separating the anterior avascular retina
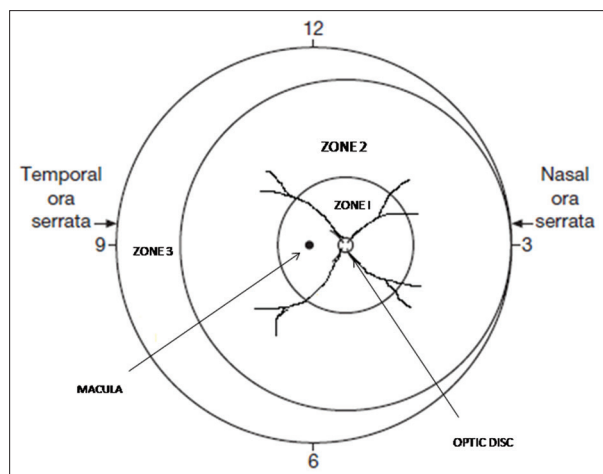

Figure 1: Zones of retinopathy of prematurity

from the vascularized posterior retina. Stage 2 is that of a ridge which is nothing; but, the demarcation line which now becomes more prominent and increases in height to extend above the plane of the retina. Stage 3 is the presence of extraretinal fibrovascular proliferation in 1–12 clock hours in addition to the presence of the ridge. Contraction of this fibrovascular proliferation at the ridge can result in partial retinal detachment (RD) which is included in Stage 4 with Stage 4a not involving the macula and Stage 4b involving the macula. Stage 5 is when this cicatricial process results in complete RD which is usually tractional; the peripheral avascular retina may, however, remain attached especially if prior laser has been done.

Epidemiology of Stage 5 Retinopathy of Prematurity

In 2008, Gilbert[6] estimated around 50,000 children aged up to 15 years were blind due to ROP. However, later Blencowe et al.[7] stated this to be an underestimation and reported up to 32,200 infants becoming blind because of ROP in 1 year (2010). Solebo et al.[8] in a recent update on childhood blindness estimated about 14 million blind children worldwide; ROP and cataract being the most common causes of preventable blindness. The prevalence of ROP in a nation not only depends on the number of premature births but also on the survival rates of the very preterm babies, neonatal care, and effective screening and treatment strategies for the prevention of ROP available. In developed high-income countries such as the United States of America and the United Kingdom, ROP is seen in very LBW infants with <28 weeks' gestation where in spite of the availability of effective ROP screening and treatment, infants progress to advanced stages because of the severity of the disease; prevalence of ROP in these countries is between 10 and 20 per 100,000 live births.[9] This is in contrast to developing and low-income countries like India where up to 86% of the infants with Stage 5 ROP may have never had a screening for ROP, highlighting the lack of awareness, and targeted screening strategies.[10] In other developing countries also such as China, Malaysia, and Taiwan where survival rates are increasing and screening protocols not yet streamlined, the prevalence rates are high.[11-13] In countries like those in Africa because of very high mortality rate, the prevalence of ROP would be <10 per 100,000 live births.[9]

Lower birth weight, lower gestational age, presence of respiratory distress, sepsis and history of blood transfusion, and supplemental oxygen are well-acknowledged risk factors for ROP.[14-16] Duration of ventilation as well as oxygen saturation has been demonstrated to influence the severity of ROP.[17,18] The supplemental therapeutic oxygen for prethreshold ROP

trial did not show any influence of change in oxygen saturation on the progression of disease, once ROP has set in.[19] Current guidelines suggest the implementation of the "Oxygen with Love" strategy for the prevention of ROP in NICUs.[20]

Pathophysiology of Stage 5 Retinopathy of Prematurity

Retinal blood supply is from two sources as follows: the choroidal vessels (outer retinal layers) and the retinal vessels (inner retinal layers). Although the development of choroid is complete by 3 months of gestation, retinal vascular development is incomplete at birth in a premature child. Retinal growth starts at 16th week of gestation, reaching the nasal ora serrata by 32 weeks and temporal by 40 weeks. Hence, more the child is premature, larger is the area of avascularity.

Two retinal vascular development processes have been recognized in the eye. (1) Vasculogenesis wherein the vessels develop *de novo* from the endothelial cells[21] and (2) angiogenesis where the blood vessel formation occurs from preexisting vessels. While vasculogenesis forms the major retinal blood vessels, the angiogenesis forms the capillary plexus in the deeper and peripheral retina.[22] The process of angiogenesis is vascular endothelial growth factor (VEGF) dependent.[23,24] Both the processes are essential for normal retinal vascular development.

In utero, there is low tissue oxygen, and the developing retina is in a state of physiologic hypoxia. The development of abnormal vasculature in ROP occurs in two phases. The initial phase of vaso-obliteration occurs in response to hyperoxia which occurs on exposure of the premature baby to environmental and supplemental oxygen necessary to treat associated conditions such as respiratory distress syndrome. The second phase occurs as a result of hypoxia due to increased metabolic demands of the maturing retina. This hypoxia results in increased VEGF resulting in vasoproliferation at the edge of the vascular retina.[25] VEGF has been implicated as a major factor in the pathogenesis of ROP.[26] Insulin-like growth factor in addition to VEGF has also been implicated.[24]

If not treated in time, proliferation of immature capillaries along with connective tissue starts at the junction of the avascular and vascular retina. These vasoproliferative cells also grow into the vitreous and contract resulting in traction on the retina.[27,28] The vasoproliferative cells also grow along the collagen fibrils in vitreous toward the posterior capsule of the lens. With increasing traction, [Figure 2a and b] the neurosensory retina detaches from the retinal pigment epithelium (RPE) resulting in tractional detachment
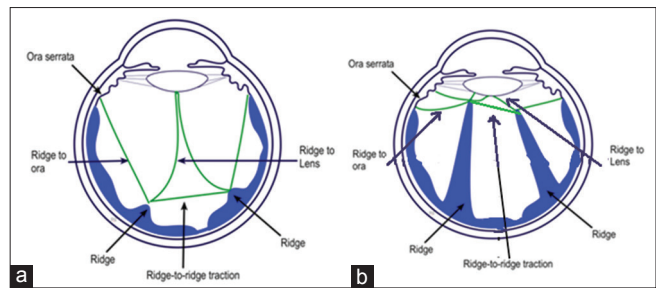
Figure 2: (a) represents beginning of RD due to various tractional forces progressing to retrolental fibroplasia (b) as seen in stage 5 disease

with a concave configuration. The effect of this traction on vascular and avascular retina is different. The vascular retina cannot stretch beyond a limit and results in detachment of the retina.[29,30] The peripheral avascular retina on the contrary can stretch significantly without getting detached.[29,30] This results in the presence of a fold between the vascularized and avascular retina which is popularly known as the "peripheral trough," a unique characteristic of Stage 5 RDs. Further contraction results in narrowing of this funnel-like RD. Varying degree of this contraction gives retinal funnel, the nomenclature of Open-Open (open anteriorly and posteriorly); Open-Close (open anteriorly and closed posteriorly); Close-Open (close anteriorly and open posteriorly); and Close-Close (both anterior- and posterior-closed funnel detachment). As proliferation continues, the fibrous tissue becomes more opaque resulting in white, dense membranes seen posterior to the lens giving Stage 5 ROP the name of retrolental fibroplasia (RLF).

Clinical Examination

Functional assessment of Stage 5 retinopathy of prematurity

The assessment of visual function in children with Stage 5 ROP is challenging. Clarkson *et al*. have suggested that an attempt should be made to look for behavior to light in these children before the surgery.[31] However, in children with bilateral RD, this can be extremely difficult. Visual-evoked potentials (VEP) have also been suggested in such cases to objectively determine the visual function.[31] The VEPs should preferably be performed when the child is awake. Although in very uncooperative children, sedation may be necessary. The role of VEP in preterm infants remains controversial.[32]

Evaluation of the anterior segment

As the proliferative tissue extends 360° behind the lens, the contraction of this RLF pushes the crystalline lens forward causing shallowing of the anterior chamber (AC), formation of posterior synechiae and anterior synechiae. This may also lead to angle-closure glaucoma.[30]

Anterior segment should be evaluated for the presence of anterior synechiae, posterior synechiae, depth of AC, and pupillary dilatation. Jabbour et al. reported the anterior segment findings of shallow AC, membrane over the pupil, and irregular pupil with posterior synechiae as significant anterior-segment findings associated with poor surgical outcome.[33]

Evaluation of posterior segment

Rarely, the RLF may not be very dense and may allow some view of the underlying retinal details.[34] Most other times, the dense RLF precludes the examination of the posterior segment. Ultrasonography is useful in studying the configuration of RD and other associated features.[31,35] The eye is assessed for the status of vitreous, retina, choroid, and axial length. The RD on B-scan should be assessed regarding configuration, presence of subretinal echoes, and location of peripheral retinal loops and cysts. The subretinal echoes can be due to the presence of serous fluid, hemorrhage, or cholesterol.[31,35,36] Gopal et al.[37] and Muslubas et al.[36] have reported the incidence of anterior- and posterior-closed funnel configuration to be as high as 81% in eyes undergoing surgery for Stage 5 ROP. The presence of subretinal opacities was observed in 9%–47% eyes.[33,35,36,38,39] These opacities have been associated with poor surgical outcomes.[38] Axial length was found to be inversely related to the severity of Stage 5 ROP.[36] Maidana et al. reported a reduction of axial length in 75% of the eyes with Stage 4 and Stage 5 ROP as compared to normal eyes.[38] Various authors have reported the anterior retinal loops in 16% to as high as 72% of these eyes.[35,36,38,40] Although ultrasonographic findings may help in predicting anatomical success following surgery, it may be difficult to discern and differentiate the retinal details from the vitreous and retinal folds.

Differential Diagnosis of Stage 5 Retinopathy of Prematurity

Stage 5 ROP most commonly presents as "leukocoria" and needs to be differentiated from ocular tumors of childhood like retinoblastoma (RB). RB can also present with RD, although it is often exudative and has a convex surface as opposed to the concave surface seen in ROP. These tumors presenting with leukocoria are typically quite large and are easily picked up on ultrasound.

Persistent fetal vasculature (PFV) can have a similar appearance to Stage 5 ROP but is usually unilateral. Other features associated with PFV include smaller size of the globe, peripheral pulled up prominent ciliary processes, and absence of a history of prematurity. Coats disease can also present as leukocoria but is also generally unilateral and has extensive subretinal lipid exudates with telangiectatic retinal blood vessels which are not

typically seen in ROP. Severe cases of familial exudative vitreoretinopathy (FEVR), Norrie disease, incontinentia pigmenti also present with neovascularization, and total RD. The absence of history of prematurity can rule out ROP in these cases.

Surgical Management of Stage 5 Retinopathy of Prematurity

Once RD has set in as seen in Stage 4 and Stage 5 ROP, surgical intervention is necessary. Surgical intervention in ROP was described as early as 1977 by Treister and Machemer.[41] Two common approaches used for surgery in Stage 5 ROP are: open-sky vitrectomy or closed vitrectomy. Scleral buckling though can be useful in Stage 4 ROP, has limited role in Stage 5 disease.[42,43]

Open-sky vitrectomy for retinopathy of prematurity

Was popularized by Hirose et al.[44] It involves trephination and removal of the corneal button followed by radial iridotomies at 6 and 12 o clock meridian, intracapsular lens extraction using a cryoprobe and dissection of the retrolental membranes in a peripheral to central fashion. Removal of the corneal button allows better visualization and removal of RLF "en block." This is followed by resuturing of the corneal button using 10-0 nylon.[44,45] Hirose et al. reported a success rate of up to 39% with this technique.[44] This technique has the advantage of allowing two-hand dissection from a larger anterior incision; however, the maintenance of intraocular pressure (IOP) during surgery may be difficult, and there is a risk of corneal rejection postoperatively after resuturing the cornea. Due to this, the focus has gradually shifted to closed vitrectomy with or without lensectomy.

Closed vitrectomy

Closed vitrectomy for Stage 5 retinopathy of prematurity without retrolental fibroplasia

This presentation is usually seen in severe cases of ROP which progress to total TRD despite peripheral retinal ablation. It is usually seen in Zone 1 or Zone 2 posterior ROP that have an open anterior and open posterior configuration of RD. As the lens is clear, lens-sparing vitrectomy (LSV) through the pars plicata is done because pars plana does not develop until 8–9 months of age.[46,47] LSV involves making three ports through the pars plicata not more than 1.5 mm from the limbus.[48] Preterm babies have much smaller eyes; hence, care has to be taken to direct the microvitreoretinal (MVR) blade toward the mid-vitreous cavity to avoid touching the lens. Furthermore, to avoid the much-elevated retina in these eyes, care must be taken to avoid going in completely with the MVR and resulting in a retinal touch or break. With the advent of microinsional vitrectomy system (MIVS), more and more surgeons prefer to do

ROP surgeries also with MIVS due to the advantages of less surgical trauma, increased patient comfort, and early postoperative recovery.[49] Gonzales et al. reported the successful use of 25G system in eyes with Stage 4 and Stage 5 disease.[50] 25G vitrectomy in ROP allows better access to the retrolental space without causing lens touch and dissection in between retinal folds without causing retinal break formation. Before making the sclerotomies, a thorough examination of the peripheral retina is done to look for areas of peripheral retinal folds. Such areas are best avoided while making sclerotomies to prevent inadvertent retinal breaks. Combination instruments, such as infusion light pipe or infusion cannula with light pipe, can be used to allow bimanual dissection. The aim of the surgery is to relieve "ridge to ora," "ridge to ridge," and "ridge to the lens" traction membranes. Vitrectomy not only helps in relieving retinal traction but also helps by reducing the VEGF load in the vitreous cavity. Posterior vitreous is very adherent to the retina, and no attempt is made to induce posterior vitreous detachment.

Gonzales et al.[50] also proposed a modification of the transconjunctival MIVS. Instead of entering transconjunctivally, ports were created after conjunctival peritomy. They hypothesized that since the pars plicata incisions in infants are made more proximal to the limbus, adequate coverage of sclerotomies will not be possible unless sutured at the end of the surgery. Suturing of the sclerotomies may also be necessary because of low scleral rigidity in these premature babies that may not allow self-sealing of the sclerotomies. Since these eyes have small interpalpebral fissure, the use of trocar and cannulas may be difficult. Sclerotomies may need to be placed closer to the horizontal meridian, to allow more room for adequate manipulation of instruments. Furthermore, a 25G MVR blade can be used to make the sclerotomies followed by direct entry with the microvitrectomy cutter or light pipe probe. Improved fluidic mechanisms of the MIVS allow prompt increase in IOP in the event of increased intraoperative bleeding resulting in reduced rates of postoperative vitreous hemorrhage. Choi et al.,[51] in their series of Stage 4 and Stage 5 ROP with 20G, reported postoperative intraocular hemorrhage in nearly 43% of cases while Gonzales et al.[50] reported postoperative vitreous hemorrhage in 13.3% of cases after 25G MIVS for Stage 4 and Stage 5 cases.

Closed vitrectomy for Stage 5 retinopathy of prematurity with retrolental fibroplasia

This is the more common presentation of Stage 5 ROP. Due to the peculiar pathoanatomy of these detachments, the principles of vitrectomy that are applicable to other forms of RD cannot be used here. Unlike LSV, the presence of retrolental tissue necessitates the removal of the lens. Furthermore, because the retina is pulled up very anteriorly, sclerotomies are made at 0.5 mm from

the limbus either through or just behind the iris root[37] to prevent inadvertent entry into the subretinal space and iatrogenic retinal break formation. Limbal approach for the surgery is also preferred to completely avoid the area of iris root especially in conjunction with the smaller gauge instruments. Kay et al.[52] have used this technique with the cannula in situ. Corneal side-port incision can also be made without the use of the trochar, and cannula system to introduce the 25G instruments directly through the corneal limbal incisions and an AC maintainer can be used in the inferotemporal quadrant.

Lensectomy is done using the microvitrectomy cutter to aspirate the lens material under low suction, once the anterior capsule is removed.[30,37] The posterior capsule is then peeled off gently using end-gripping intraocular forceps.[37,48] This is followed by cruciate incisions into the RLF to expose the underlying retina [Figure 3a]. The preretinal tissue is removed completely without retinal break formation using 23/25G intraocular forceps and scissors using bimanual dissection under coaxial illumination of the microscope. The dissection is continued until the posterior funnel of RD is opened up with removal of the fibrous stalk from the optic nerve head that holds the retina along the central axis [Figure 3b and c]. Using the improved fluidics of MIVS, IOP is rapidly increased in case of sudden bleeding and any intraoperative bleeding blood vessels can be coagulated. "Peripheral trough" (formed between the peripheral avascular retina and retinal fold from ridge) is then opened-up all around by careful dissection to remove the fibrous tissue formed between the peripheral-attached avascular retina and the retinal fold from the ridge [Figure 3d]. This is done using the microvit and/or curved scissors under binocular indirect ophthalmic microscope (OCULUS Optikgeräte GmbH, Germany) for wide-angle view intraoperatively.
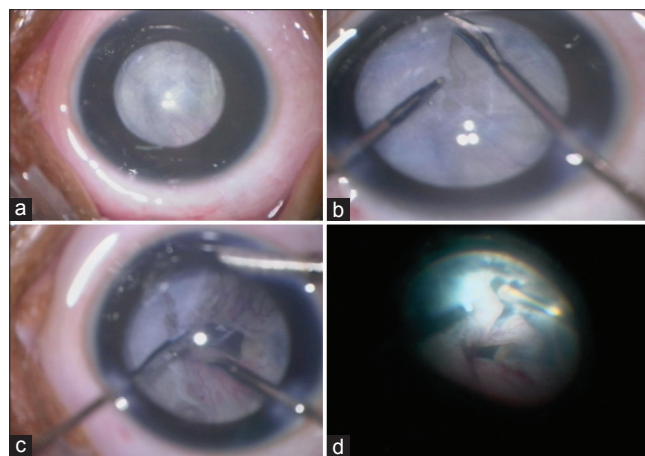
Figure 3: Steps in lensectomy and vitrectomy for Stage 5 retinopathy of prematurity. (a) retrolental fibroplasia as seen in Stage 5 retinopathy of prematurity (b) formation of cruciate incisions into the retrolental fibroplasia (c) removal of the retrolental fibroplasia in all quadrants (d) opening up of the peripheral trough using microvitrectomy cutter under the binocular indirect ophthalmic microscope

The surgery is completed without any retinal break formation. The retinal break is identified during surgery by the presence of Schlieren [inflow of straw-colored fluid from the subretinal space; Figure 4]. The use of adrenaline (1:1000 dilution in 0.1 ml or 1:1000,000 in 0.2 ml) in infusion line can help to keep the pupil well dilated.[30,37] In cases with posterior synechiae, the use of iris retractors is done. The use of MIVS allows the iris to be left undisturbed. After meticulous relief of all traction, the partial fluid gas exchange may be done though not essential. Subretinal fluid (SRF) drainage is not done.[30] These sclerotomies need to be sutured in all cases with 10-0 nylon or 10-0 vicryl.

Removal of the preretinal tissue is usually done from the center to the periphery. In a pilot study by Gopal and Sharma,[53] the dissection was initiated from the periphery until the center with good results; however, it may not be possible in all cases.

Complications of Surgery

Postoperative complications of surgery include retinal break formation, vitreous hemorrhage, secondary glaucoma, corneal clouding, cataract, strabismus, and phthisis. Most frequently reported complication is that of glaucoma following surgery with incidence up to 33.3%.[37,51,54-58] In one of the recent reports, the risk of postoperative secondary glaucoma was higher in eyes that underwent lensectomy during the surgical procedure.[58]

Recurrence of RD has been observed in 22% of cases in Stage 5 as compared to 5% in Stage 4.[59] This highlights the importance of prolonged follow-up of these eyes even after successful reattachment [Figure 5].

Surgical Outcomes

The surgical outcomes can be considered for two parameters – anatomical success and functional success.
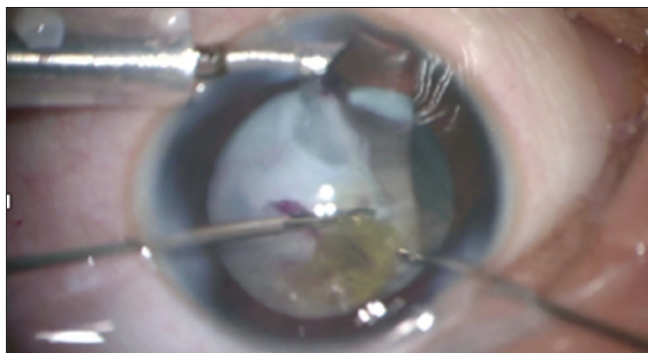

Figure 4: Intraoperative picture of inflow of straw-colored fluid (Schlieren) from subretinal space due to the presence of underlying retinal break

Anatomical success

Anatomical success after surgery for Stage 5 ROP has been commonly defined as the attachment of the posterior retina. Generally, the rates of reattachment have been reported as disappointing following surgery for Stage 5 ROP ranging between 13% and 45.5%.[30,37,48,54,55,60,61] Fuchino et al.[62] reported up to 59% anatomical success while Machemer and deJuan[30] in their 121 eyes with Stage 5 ROP reported partial attachment in 40% of the eyes and complete attachment in only 9% of the eyes post-closed vitrectomy. Gopal et al.[37] reported an anatomical success rate of 22.5% with lensectomy and vitrectomy in 96 eyes with Stage 5 ROP and Shah et al.[48] compared the anatomical success rates in Stage 4 and Stage 5 and reported anatomic success after surgery in Stage 5 of 14% as compared to 90% in Stage 4A group. Cusick et al.[61] in their series of 608 eyes with Stage 5 ROP demonstrated a 28% surgical success rate. Lakhanpal et al.[60] reported a success rate of 45.5% after LSV in Stage 5 ROP in 33 eyes. About 63.6% of their eyes were of open-open configuration, thus suggesting that the stage at which surgery is performed is an important prognostic factor. Open-open or partially open funnel configurations have been reported to fare better than closed configuration detachments by other authors too.[30,37,60,63] Gopal et al.[37] attributed the poor anatomical outcome to the presence of a narrow-narrow funnel configuration at the time of surgery in 81.3% of eyes. Choi et al.[63] found a better outcome (44.4%) in open funnel type as compared to closed funnel type (15%) RD.

Another factor which has been significantly associated with improved outcomes is age at surgery. Machemer et al.[30] and Cusick et al.[61] had reported a higher success rate when babies were operated after 6 months of age. Gopal et al.[37] and Fuchino et al.[62] have suggested that since the disease is more vascularly active in babies <6 months of age, operating within 6 months has
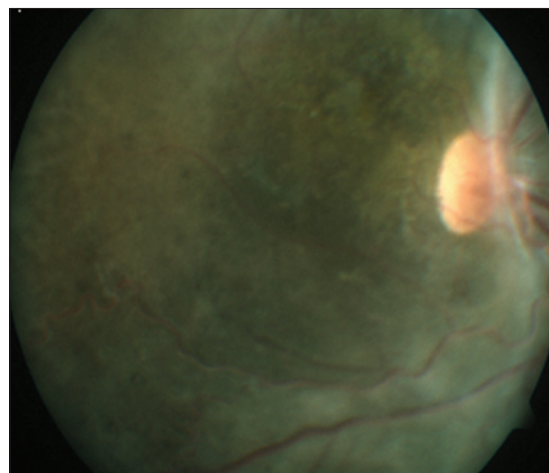
Figure 5: Postoperative fundus picture showing reattached retina following lensectomy and vitrectomy for a patient with Stage 5 retinopathy of prematurity

marked risk of postoperative hemorrhages. This can, however, be reduced by preoperative or postoperative use of bevacizumab.[64]

Gadkari et al.[34] reported better anatomical results in eyes with minimally fibrotic Stage 5 ROP (those eyes that had a translucent RLF with visibility of the underlying retinal vessels and absence of anteriorly rotated ciliary processes). The presence of iatrogenic breaks intraoperatively has usually resulted in poor results.[37,60] A study comparing the ocular features with the surgical outcomes has reported the presence of two or more quadrants of plus disease and 6 clock hours of ridge elevation to be associated with persistent RD.[54]

Fuchino et al.[62] have compared the retinal attachment rates in patients with shallow and deep ACs and did not find any significant differences. Jabbour et al.,[33] however, found anterior-segment features such as anterior and posterior synechiae associated with poor outcome.

Functional success

Measurement of visual acuity in these children is extremely difficult, and visual improvement after a successful Stage 5 surgery may be extremely slow and limited. Even though various surgeons have reported the successful anatomical outcome in up to 50% of cases, functional improvement in these eyes has been largely disappointing. Gopal et al.[37] reported mobile vision in 2 out of the 96 eyes studied. They suggested that the detached retina undergoes degenerative changes with time, and even the reattached retina remains thin leading to possible loss of functionality. Perception of light (PL) has been reported in 21%–81.25% of patients.[48,56,57,61,65] In the series reported by Shah et al.,[48] three babies out of the 14 with Stage 5 had PL vision postoperatively. Cusick et al.[61] reported a PL vision in 59%, no light perception in 26%, hand movements in 10%, and better than 5/200 vision in 4% eyes out of the 183 eyes in whom visual function could be recorded. Fuchino et al.[62] and Hirose et al.[44] reported better visual outcome in these children if they are operated before 1 year of age. Fuchino et al.[62] also reported better vision in some Stage 5 eyes which underwent LSV with one of the eyes gaining up to 20/25 vision after surgery. The visual outcomes were better in eyes operated earlier, did not have much subretinal exudation and RPE alteration and a low iron concentration in the SRF.[62,66]

Form identification was seen in up to 10%–20% of patients.[51,56,67] Seaber et al.[56] evaluated the long-term visual outcomes in 51 vitrectomized ROP eyes and found that ambulatory vision could be achieved in five eyes and 11 eyes had PL and form identification was present especially if the objects are lit. Similar outcomes were reported by Karacorlu et al.[57] who found that

Stage 5 eyes could achieve an average vision of 20/4000. Visual deprivation in early months also may affect the development of cognitive function early on even after successful reattachment. Hence, prolonged efforts for visual development should not be given up too soon.

The anatomical and functional outcomes and the complications, following surgery as reported by various authors is summarized in Table 1.

Use of Pharmacological Adjuncts

Plasmin-assisted vitrectomy

One of the main causes of poor visual outcome in these eyes is the presence of tough adhesion between the retina and vitreous that does not allow complete separation of the posterior vitreous. Plasmin is known to degrade glycoprotein which is the major adhesive between the cortical vitreous and internal-limiting membrane.[68] Autologous plasmin has been used by surgeons to facilitate complete vitreous separation in Stage 5 ROP.[65,69] Autologous plasminogen (AP) is purified from the patient's plasma and activated with urokinase.[69] 0.03–0.22 IU of AP in a volume of 0.1–0.15 ml is then injected into the vitreous cavity intraoperatively after removal of the RLF, and further dissection is done after 10–15 min. Tsukahara et al.[69] reported adequate relief of traction in all six cases subjected to this method without an increase in the retinal break formation. Wu et al.[65] have shown improved results with autologous and maternal plasmin in eyes with primary as well as reoperated Stage 5 disease.

Intravitreal triamcinolone

The use of intravitreal steroids during vitrectomy has been also investigated by Lakhanpal et al.[70] especially in vascularly active eyes with Stage 5 disease. In their series of eyes lensectomy and vitrectomy was performed with intravitreal triamcinolone acetonide (IVTA) in 10 eyes with vascularly active Stage 5 ROP. After the closure of sclerotomies, 2.0 mg/0.05 ml of IVTA was injected onto the retinal surface. About 60% eyes (6 out of 10) achieved anatomical success as compared to none in those eyes where IVTA was not used.[70] The authors also observed a rapid resolution of SRF in such cases with no increase in fibrosis. Inhibition of VEGF and deceased vascular permeability secondary to steroids may be the possible underlying mechanisms, although this method has not been vastly used by many surgeons.

Role of Genetics in Stage 5 Retinopathy of Prematurity

The variability of presentation and heterogeneous response to treatment has led researchers to look for

Table 1: Anatomical, functional outcomes and complications for surgery in Stage 5 ROP

Study	Surgery	Anatomical success rate n (%)	Visual Outcome	Follow up	Complications
Trese et al.[66], 1986	20 G L+V	85 (48)	26 eyes showed lid closure to bright light, 18 eyes could follow light, 10 eyes could grasp colorful object, 15 eyes showed head turning and grasping of penlight in their visual field and 6 eyes showed lighted shape identification	6 months	Not reported
Machemer et al.[30], 1990	20 G L+V	121 (40)	16 eyes out of 101 eyes (16%) achieved visual acuity HM or better	2 years	Not reported
Choi et al.[63], 1994	20 G L+V	38 (29)	Fixation and following behaviour in 7 eyes (18.4%), PL in 15 eyes (39.5%), No PL in 16 eyes (42.1%)	24 months	3 eyes had persistant vitreous hemorrhage
Seaber et al.[56], 1995	20 G vitrectomy	51 eyes with attached retina included in study	5 eyes had form identification with ambulatory vision, 4 had form detection, 10 were able to follow light, 6 could localise light, 11 had PL and 15 had no PL	61 months	3 eyes developed glaucoma, 7 eyes developed corneal opacities, 7 eyes developed optic atrophy, 9 eyes developed pupillary abnormalities
Yuki Fuchino et al.[62], 1995	20 G vitrectomy	49 (59)	Out of 21 eyes, 1 eye 20/25, 5 eyes 20/200 to 20/25, 7 eyes 20/2000 to 20/200, 3 eyes HM, 4 eyes PL, 1 eye No PL	2 years	Not reported
Hittner et al.[67], 1997	20 G L+V	45 (76)	9 eyes had form identification, 5 eyes had 20/600 to 20/4000, 4 eyes had better than 20/400	84 months	Not reported
L Gopal et al.[37], 2000	20 G L+V in all except one case	96 (22.5)	2 children achieved mobile vision	72 months	Retinal dialysis occured in 14 eyes (14.6%), posterior retinal breaks in 3 eyes (3.1%),10 eyes (10%) developed secondary glaucoma
Hartnett et al.[54], 2003	20 G L+V in 11 eyes, SB in 3 eyes	14 (28.6)	Not reported	31 months	Corneal clouding and glaucoma in 1 eye (7%)
Cusick et al.[61], 2006	20 G vitrectomy	608 (28)	Out of 183 eyes, 4 (2%) achieved>20/200, 4 (2%) between 5/200 & 20/200, 19 (10%) HM, 108 (59%) PL, 48 (26%) no PL	44 months	31 eyes (5%) developed corneal opacity, 17 eyes (3%) developed secluded pupil and 20 eyes (3%) became phthisical
Lakhanpal et al.[70], 2006	IVTA assisted	10 (60)	6 eyes (60%) showed fixation and following behaviour	26 months	Nil
Gonzales et al.[50], 2006	25 G L+V	2 (0)	Not reported	4.6 months	Nil
Young Suk yu et al.[55], 2006	20 G LSV	4 (25)	All 4 eyes had no light perception	2.2 years	2 eyes (50%) developed glaucoma, 1 eye (25%) developed cataract and 1 eye (25%) developed Vitreous hemorrhage
Lakhanpal et al.[60], 2006	20 G LSV	33 (45)	Not reported	32 months	1 eye (3%) developed glaucoma, retinal tears occured in 21% eyes, 13 eyes (39%) underwent secondary lensectomy
Tsukahara et al.[69],2007	Plasmin assisted	6 (100)	Not reported	12 months	Nil
Wu WC et al.[65], 2008	Plasmin assisted vitrectomy	80 (69)	6 eyes (7.5%) had pattern vision, 3 (3.8%) showed fixation and following behaviour, 56 (70%) had PL, 11 (13.8%) no PL	49 months	22 eyes (27.5%) reproliferation, 6 (7.5%) developed glaucoma, 4 (5%) had corneal decmpensation, 4 (5%) phthisis bulbi, 4 (5%) vitreous hemorrhage, 3 (3.8%) band keratopathy, 3 (3.8%) pupillary membrane, 2 (2.5%) cataract
Shah et al.[48], 2009	20 G L+V	14 (14)	PL present in 3 eyes	32 months	Posterior retinotomy was commonest complication followed with dialysis and giant retinal tear

Contd...

Table 1: Contd...

Study	Surgery	Anatomical success rate n (%)	Visual Outcome	Follow up	Complications
Choi et al.[51], 2011	LSV	8 (13)	1 eye achieved form vision, 7 eyes had no PL	5.6 years	3 eyes developed corneal opacity, 3 eyes developed cataract, 4 eyes developed glaucoma, 4 eyes developed intraocular hemorrhage, 2 eyes developd strabismus and 1 eye had microophthalmia
Gadkari et al.[34], 2016	20 G L+V	22 (54.5)	2 eyes achieved 20/2700 to 20/960 and 10 eyes could follow light,	6 months and above	Not reported
Karacorlu et al.[57], 2017	20 G L+V	31 (42)	11 eyes achieved 20/4000, 2 eyes had fixation and following behaviour and 18 eyes had PL or No PL	5 years	6 eyes (19%) developed corneal opacity, 9 eyes (29%) glaucoma, 7 eyes (23%) strabismus and 3 eyes (10%) phthisis
Nudleman et al.[58], 2017	LSV	21 (81)	Not reported	0.85 years	7 eyes (33%) developed Glaucoma

N=Number of eyes, L=Lensectomy, V=Vitrectomy, PL=Perception of Light, HM=Hand movements, SB=scleral buckling, LSV=Lens sparing vitrectomy

underlying genetic predisposition for severe ROP. ROP is clinically similar to FEVR except for the history of prematurity. Recent studies suggest a genetic predisposition to ROP in patients who have defect in the Wnt receptor signaling pathway particularly in norrin cystine knot growth factor (NDP) and Frizzled 4 (FZD4) genes similar to the ones seen in FEVR.[71] Genetic variants of FZD4 and low-density lipoprotein receptor-related protein 5 have also been reported in the Japanese population in cases of advanced ROP.[72] Thus, suggesting a role of genetic factors apart from the environmental factors. Recently, a group of authors have identified strong correlation of ROP with newer genes, namely the variants of complement factor H, C-X-C chemokine receptor type 4, Fibulin 5, complement factor B, and cholesteryl ester transfer protein (CETP).[73] Among these CETP was found to be a risk factor, and others were protective indicating the involvement of complement pathway.

Medicolegal Aspects of Stage 5 Retinopathy of Prematurity

There is a growing need to create ROP awareness among the parents and healthcare providers. It is important for pediatricians, neonatologists, obstetricians, and ophthalmologists to make sure screening, follow-up, and timely intervention for ROP is done. Although few severe cases may progress to Stage 5 ROP even after regular screening examinations and laser treatment, not initiating ROP screening is considered a case of negligence. It is important for NICU's to have a screening system in place that ensures that the babies receive timely examinations and follow-up treatment when required. Protocols should include notifying parents, guardians, hospitals, and pediatricians when a baby fails to be brought in for an appointment. RetCam (Clarity Medical Systems, Pleasanton, CA) imaging can be helpful in documenting ROP.

Conclusion

Our understanding of the pathogenesis and surgical management of Stage 5 ROP has come a long way. Surgery for Stage 5 has shown anatomic reattachment in 20%–50% of cases. Even though the measurable visual acuity may remain poor, the parents of these children do report some useful vision which continues to slowly improve. This vision can make a world of difference to a blind child. Furthermore, an anatomically attached retina always gives the hope of some future viable option-like gene therapy, stem cells, or retinal prosthesis. Till definite steps are taken to bring all preterm babies into the network of screening and timely treatment, surgery for Stage 5 ROP is here to stay. This is the only hope for these children. The most important aspect of the treatment for Stage 5 ROP is the education of parents regarding the limited visual outcomes that may benefit a small proportion of eyes undergoing surgery and need for prolonged follow-up.

Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

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