Original Article

Short-term incidence and management of glaucoma after successful surgery for stage 4 retinopathy of prematurity

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Purpose: The purpose of this study is to describe the short-term incidence, clinical features, and management of glaucoma in children after successful surgery for stage 4 retinopathy of prematurity (ROP). **Methods:** The retrospective study included all eyes undergoing successful surgery for stage 4 ROP with good outcomes at a tertiary eye care center between June 2014 and June 2016. Cases developing postoperative glaucoma underwent examination under anesthesia for measurement of intraocular pressures (IOP), corneal diameters, Retcam-assisted fundus imaging, and gonioscopy. Outcomes of glaucoma management were evaluated. **Results:** Hundred eyes of 70 babies underwent successful surgery for stage 4 ROP (with postoperative attached retina, and minimal sequelae) with minimum follow-up of 15 months. Six eyes (6%) developed postoperative glaucoma. Of these, four eyes had undergone lens-sparing vitrectomy and two were managed with lensectomy and vitrectomy (LV). Median time duration for development of glaucoma after primary vitreous surgery was 17.5 weeks. Two cases could be managed with topical IOP-lowering agents alone, whereas four required filtering surgeries (trabeculotomy with trabeculectomy and 0.04% mitomycin C [MMC] application). Average IOP decreased from 25 ± 2.36 to 12.2 ± 2.05 mmHg at 12 months from glaucoma diagnosis. **Conclusion:** Glaucoma is a potential adverse event following successful vitreous surgery for stage 4 ROP. A combined trabeculotomy–trabeculectomy along with MMC gives favorable outcome.

Key words: Combined glaucoma surgery, glaucoma in retinopathy of prematurity, goniodysgenesis, retinopathy of prematurity, stage 4 retinopathy of prematurity, trabeculectomy, trabeculotomy, vitrectomy

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Retinopathy of prematurity (ROP) is a major cause of childhood blindness in middle income countries.[1] Early stages of ROP are managed with laser photocoagulation and usually have a good visual outcome. Advanced stage 4–5 ROP with retinal detachment requires surgical intervention.

Development of postsurgical complications poses additional challenges in achieving long-term satisfactory results. Disease sequelae such as retinal drag and falciform fold as well as complications such as vitreous hemorrhage, rhegmatogenous retinal detachment, cataract, squint, and glaucoma are known causes for poor outcome. Glaucoma after ROP has been reported previously with prevalence of 1.67% at 6 years in babies enrolled in ETROP study and was found to be more common in eyes receiving delayed laser.[2] A type of ciliary block glaucoma was reported in regressed ROP cases with mild sequelae by Kushner *et al*.[3] which was treated with vitreous or lens removal. Secondary glaucoma has been described in advanced stages of ROP,[2] although development of secondary glaucoma with surgically treated ROP is not a common occurrence.[4-6]

Secondary glaucoma adds to the morbidity of ROP itself, thereby reducing future prospects for good functional results. Previous studies on the topic included both stage 4 and 5 ROP cases, although surgical results for the two conditions vary greatly. Whereas most operated stage 4 cases have good anatomic and functional outcome, stage 5 cases rarely fare well.

Typically, after good surgical outcomes in stage 4 ROP, surgeons continue to review the retinal status on follow-up but fail to monitor for glaucoma. We describe here clinical features and management of secondary glaucoma in six eyes of six babies, which developed in a series of 100 successfully operated eyes with stage 4 ROP.

Methods

This study is a retrospective review of successful surgically treated cases of stage 4 A–B ROP between June 2014 and June 2016 at a tertiary eye care center that developed secondary glaucoma. The study adhered to the tenets of Helsinki. A signed informed consent was obtained from the parents prior to every procedure.

A review of medical records of all operated stage 4 ROP cases (in the defined time period) which had good postoperative outcomes (with postoperative attached retina, and minimal

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sequelae at last follow-up) was done. Hundred eyes (90 stage 4A and 10 stage 4B) of 70 babies were included in the study. All eyes had undergone laser photocoagulation to peripheral avascular retina within two days of diagnosis of ROP.

A suture-less 25-G lens sparing vitrectomy (LSV) was performed for stage 4A/B ROP by a single surgeon (PC). LV was performed in selected cases with high peripheral tractional retinal detachment necessitating limbal corneal entry. Fluid air exchange was performed at the end of surgery. Silicone oil, viscoelastic agents, or expansile gases were not used for tamponade in any case.

The postoperative treatment consisted of topical gatifloxacin 0.3% QID for 5 days whereas topical prednisolone acetate 1% QID, homatropine 2% QID, and carboxy methyl cellulose 0.5% QID were tapered over 3 weeks. Regular follow-up every 2 weeks for first 2 months, and then 3 months, was carried out. Wide field fundus imaging (Retcam 3, Clarity Inc. USA) was performed in all cases. Fundus evaluation including optic nerve head (ONH) evaluation was done in all cases by a retina expert.

Cases with suspicion of glaucoma and suggestive signs and symptoms such as increased ONH cup size, increased corneal diameters (CDs), corneal edema, and persistent watering underwent a detailed examination by a glaucoma expert (performed while the child was sleeping) that included intraocular pressure (IOP) measurement (Tono-Pen Avia, Reichert, Inc., USA) and ONH evaluation. For our study, we used Tono-Pen for IOP measurement as it is easy to use in children, who are sleeping or under sedation, and is reported to be accurate in eyes with previous vitrectomy.[5] The Tono-Pen readings were repeated at least 3 times and the average values within 2 mmHg were taken for analysis.

Medical treatment was initiated first in all cases and a baseline examination under anesthesia (EUA) was performed that included IOP measurement (Perkins), fundus evaluation, CDs (with calipers), and gonioscopy (Retcam 3/Swan Jacob lens). Repeat IOP measurements (sleeping IOP with Tono-Pen) and fundus evaluation (Retcam 3) were performed on an outpatient basis.

An EUA was performed after 2 months of medical therapy. In cases not responding to medical treatment (IOP >21 mmHg, persistence of corneal edema and increase of ONH cupping or CDs), surgical intervention was carried out. Glaucoma surgery consisted of trabeculotomy and trabeculectomy with 0.04% mitomycin C (MMC) application (subconjunctival and subscleral) by a single surgeon. In the initial postoperative period, sleeping IOP measurements were performed followed by a detailed EUA (as described previously) every 3 months.

Results

Hundred eyes (90 stage 4A and 10 stage 4B) of 70 babies which underwent stage 4 ROP surgery with good postoperative outcomes were included in the study. Development of postoperative glaucoma was seen in 6% cases (6 of 100 eyes), which included five eyes operated for stage 4A (5.56%) and one eye for stage 4B ROP (10%). The demographic and baseline examination data including details of primary retinal surgery are presented in Table 1. Data pertaining to presentation and management of glaucoma are presented in Table 2.

The mean birth weight of the babies was 1336.34 ± 158.6 g (range 1250–1600 g) and the mean gestational age was 29.34 ± 1.21 weeks (range 28–31 weeks). The mean postmenstrual age at diagnosis and treatment of ROP, surgery

Table 1: Baseline and ROP surgery details of the 6 babies with postoperative glaucoma

Case	Sex	Eye	BW (g)	GA (w)	PMA (w)*	Stage	ONH	1st VIT	PMA (w)†	2nd VIT
1	F	OS	1228	29	34	4A	0.3	LSV	38	-
2	M	OS	1600	30	37	4A	0.4	LSV	38	-
3	M	OD	1380	31	36	4A	0.4	LSV	39	LSV
4	M	OD	1400	30	45	4A	0.4	LSV	46	-
5	M	OS	1250	28	48	4B	0.3	LV	48	-
6	F	OS	1160	28	39	4A	0.4	LV	43	-

BW=Birth weight in grams, GA=gestational age in weeks, PMA=postmenstrual age in weeks, ONH=Optic nerve head cupping at baseline exam, VIT=type of vitreous surgery, LSV=lens sparing vitrectomy, LV=lensectomy and vitrectomy. *PMA at diagnosis; †PMA at vitreous surgery

Table 2: Profile of development of glaucoma and management of the 6 babies with postoperative glaucoma

Case	PMA (w)*	INT (w)	At glaucoma diagnosis			TX	FU (M)	At last follow-up		
			IOP (mmHg)	ONH	CD (mm)			IOP (mmHg)	ONH	CD (mm)
1	42	4	24	0.9	11	MED (1)	24	12	0.5	11
2	58	20	24	0.7	13	MED (1) + SX	27	14	0.6	13
3	54	15	22	0.8	12	MED (1) + SX	25	12	0.8	12
4	53	7	25	0.8	11	MED (2) + SX	38	12	0.6	11
5	68	20	26	NA	12	MED (2)	15	9	0.8	12
6	113	70	29	0.8	13	MED (2) + SX	28	14	0.7	13

PMA=Postmenstrual age in weeks, INT=time duration between vitreous surgery and onset of glaucoma in weeks, IOP=intraocular pressures in mmHg, ONH=optic nerve head cupping, CD=horizontal corneal diameters in millimeters, TX=glaucoma treatment strategy, MED=medical management with topical drugs with number of drugs in brackets, SX=filtering surgery, that is, trabeculotomy and trabeculectomy with MMC 0.04%, FU=total follow-up in months from first vitreous surgery, NA=could not be assessed. *PMA at glaucoma diagnosis

for ROP, and diagnosis of glaucoma were 39.83 ± 5.5 weeks (range 34–48 weeks), 42 ± 4.34 weeks (range 38–48 weeks), and 64.67 ± 25.12 weeks (range 42–113 weeks), respectively. The median time interval between primary vitreous surgery and diagnosis of glaucoma was 17.5 weeks (range 4–70 weeks).

The mean duration of follow-up after primary vitreous surgery and detection of glaucoma was 26.16 ± 7.41 (range 15–38 months) and 19 ± 5.1 months (range 12–23 months), respectively.

All babies included in the study presented with advanced stages of ROP requiring surgery for retinal reattachment. LSV and LV were performed in 92 eyes (86 stage 4A and 6 stage 4B) and 8 eyes (4 stage 4A and 4 stage 4B), respectively. A total of six eyes developed glaucoma (five stage 4A and one stage 4B). Four stage 4A eyes underwent LSV with one eye requiring repeat vitrectomy due to recurrent vitreous hemorrhage. Two eyes, one stage 4A and the other stage 4B, were managed with LV. None of the operated eyes showed signs of congenital glaucoma or raised IOP preoperatively. Increased corneal size and mild corneal haze were seen in all cases and it was the larger eye size that raised an alarm for the parents as well as the treating ophthalmologist. Classical Haab's striae were seen in one case. Examination findings included increased CD compared to fellow eye (all eyes) and IOP more than 21 mmHg in all cases. Advanced ONH cupping could be documented in all eyes (one case had significant media haze precluding fundus evaluation at the initial examination that later cleared). Gonioscopy revealed features suggestive of goniodysgenesis such as high insertion of iris and presence of iris processes in all eyes [Fig. 1a and b].

Medical management was initiated first in all cases and response was assessed at 2 months after which nonresponders were planned for surgical intervention without further delay due to the advanced stage of glaucoma. Topical betaxolol 0.25% twice a day alone (3 cases) or in combination with latanoprost 0.005% (3 cases) were prescribed depending upon presenting IOP and clinical features. Two cases showed good response to topical medications (cases 1 and 5). Both showed corneal clearing and lowering of IOP. Case 1 had a peculiar course with a sudden increase in ONH cupping from 0.3 to 0.9 in matter of 4 weeks after vitreous surgery [Fig. 2a-d] that showed a dramatic reversal to 0.6 at 2 months and 0.5 at 6 months with single topical antiglaucoma treatment. This was maintained till the last follow-up.

Four eyes, however, did not respond well to medical therapy and had to undergo surgical intervention in the form of combined trabeculectomy with trabeculotomy. All eyes had an uneventful postoperative period with good IOP control, corneal clearing, and stabilization or reversal of ONH cupping. No additional procedures or topical drugs were required for IOP maintenance till the last follow-up in all eyes.

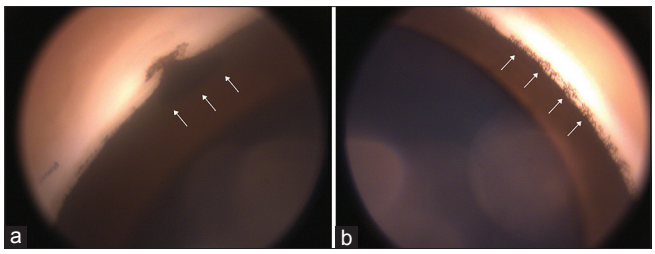

Figure 1: (a) Gonioscopy image of case 2 shows a patent iridectomy (arrows) and (b) elongated iris processes and an immature trabecular meshwork (arrows) are seen in the same case

Discussion

Postoperative glaucoma after stage 4 ROP surgery is poorly reported in literature. Documentation of features of glaucoma has not been consistently described in babies operated for advanced stages of ROP. Moreover, previous studies have relied upon IOP measurement as the sole criterion for diagnosing glaucoma.[5,6] We did not measure IOP in all our cases and the diagnosis of glaucoma was clinical, although all diagnosed cases of glaucoma had IOPs greater than 21 mmHg.

Detection of glaucoma poses certain challenges in preterm babies. Use of IOP measuring techniques on a routine basis in all postoperative ROP cases may not always be feasible in a high-volume setting. This leads to delayed diagnosis of glaucoma that manifests as increased corneal size, corneal haze, and even development of Haab's striae. Since the premature eye is growing at a rapid pace, even small changes in IOP can lead to a sudden increase in eye size. The plasticity of the growing eye may also explain the advanced glaucomatous cupping seen in such cases that reverts back to a certain extent on controlling the IOP, as seen in case 1 [Fig. 2a-d] of our study. Another associated complication is anisometropia that may ultimately lead to development of amblyopia in the affected eye.

We found an apparent increase in corneal size (compared with the fellow eye) and increased ONH cupping to be the primary reason for suspecting glaucoma in our series, although mild corneal haze and watering were also present in some children as the presenting complaint. As most of the cases had delayed onset of glaucoma when the follow-up exams were being done at 3-month intervals, such cases have a tendency to be missed early in the course. Therefore, we believe, it is

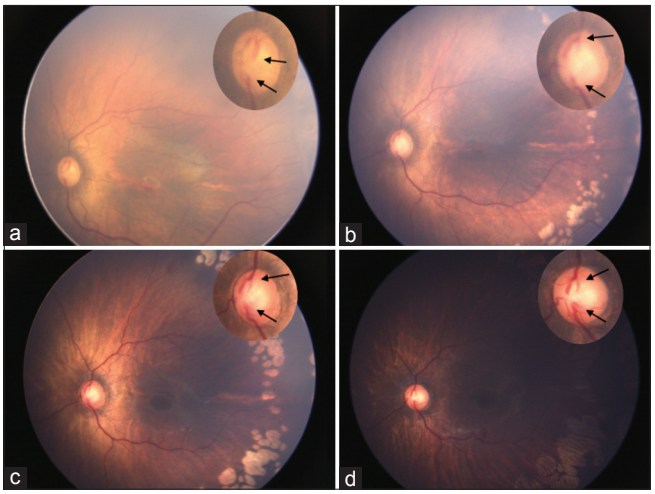

Figure 2: Serial fundus images of the left eye of case 1 which shows (a) 0.3 cupping of ONH (inset/arrows) at PMA 36 weeks, 2 weeks after laser treatment. (b) 4 weeks after vitreous surgery, at PMA 42 weeks, 0.9 ONH cupping is seen (inset/arrows) was noted. Subsequently, (c) 2 months later, at PMA 50 weeks, ONH cupping reduced to 0.6 (inset/arrows). Fundus picture taken after six months of topical glaucoma therapy (d) shows decrease in ONH cupping to 0.5 (inset/arrows)

important not to miss even the smallest changes in corneal size and ONH cupping that might indicate development of glaucoma. Regular measurement of IOP may also help in diagnosing these cases early.

Iwahashi-Shima *et al*.[5] described the range of time duration for IOP elevation as 2–4 weeks after surgery for ROP, whereas a recent chart review by Nudleman *et al*.[6] with long-term follow-up reported a much greater time interval between the vitreous surgery and development of glaucoma. In our series, the cases in LSV group developed glaucoma at mean 11.5 weeks (4–20 weeks) post-vitreous surgery compared with mean 45 weeks (20–70 weeks) in those who had lensectomy with vitrectomy. While this could be a coincidental finding, it is difficult to explain why eyes with lens extraction developed glaucoma in the late postoperative period. One possibility for the early development of glaucoma could be a steroid response in the LSV group, although both LSV and LV eyes received the same potency and duration of steroids. Postsurgical glaucoma was described in five ROP babies after successful open sky vitrectomy by Hartnett *et al*.[7] One of these cases developed shallow anterior chamber with narrowing of angles due to extensive peripheral anterior synechiae. They attributed this to possible surgical trauma and collection of blood and fibrin after surgery. The other four eyes had more than 180 degrees open angles. Surgical trauma, goniodysgenesis, and halt in development of the immature angles were postulated to be the causes.

Postsurgical IOP elevation and subsequent development of glaucoma in eyes of ROP children in our series can be ascribed to multiple causes. Steroid response has been identified as a major risk factor for development of IOP elevation and is especially pronounced in children[8] and in eyes with goniodysgenesis.[9] The usual rise in IOP after topical steroid instillation occurs after 2–4 weeks and is found to subside after 1–4 weeks of stopping treatment.[10] In case 1 with early development of glaucoma, steroid response could have been the primary cause for IOP elevation. Moreover, the fact that this case could be managed with topical glaucoma therapy alone points toward a transient nature of IOP elevation and a possible steroid response. However, rest of the cases developed glaucoma well outside the established "window period" of steroid response.

Various authors have described the effects of vitrectomy on IOP changes in adults, although a definitive causal relationship has not been well established. Koreen *et al*.[11] highlighted the increased risk of open-angle glaucoma after uncomplicated pars plana vitrectomy (PPV) that was further increased after lens extraction. Chang *et al*.[12] hypothesized the role of increased oxygen delivery to the trabecular meshwork leading to oxidative damage to be one of the causes of increased IOP and a high incidence of post-vitrectomy glaucoma (15–20%) in adults. However, this retrospective study included cases with many confounding factors such as use of different tamponade agents. Lalezary *et al*.[13] reported an incidence of rise in IOP by 4 mmHg as 7% at the end of 4-year follow-up in their study with better case selection and concluded that uncomplicated PPV even with lens extraction did not lead to glaucoma.

The only common denominator in all eyes in our series was the presence of an immature trabecular meshwork with high insertion of iris. This finding in preterm babies with ROP was recently reported in a study by Chang *et al*.[14] that showed presence of a narrower anterior chamber angle along with more anteriorly curved iris insertion than in normal full-term neonates. However, they did not comment on any association of their findings with future development of glaucoma. Even in our study, it is also not possible to differentiate these cases from delayed onset congenital glaucoma which tend to have a similar presentation and to comment on the future affliction of the fellow eyes. But in the light of our findings which include features suggestive of goniodysgenesis in all the affected eyes and an increased incidence of glaucoma in eyes undergoing vitrectomy compared with laser treated eyes,[2] it seems prudent to label these cases as secondary glaucoma. Moreover, these findings also force us to consider a possible role of the vitreous surgery precipitating a decompensation of the immature trabecular meshwork leading to development of glaucoma in these small babies. Various factors related to surgery such as IOP fluctuations or postoperative inflammation may be responsible for an early and significant damage to the trabecular meshwork leading to development of glaucoma.

We initially treated all patients with topical antiglaucoma medications. Two of the cases, one that underwent LSV and the other LV, could be managed successfully with topical medications alone. Four cases, however, required surgical intervention. Hartnett *et al*.[7] have previously described use of topical timolol as the sole agent in five of their cases, with a need for additional procedures in two eyes. They noted that in most of their cases, conjunctival scarring due to primary surgery (open sky vitrectomy) posed greater challenges in performing a successful filtering surgery. Instead, they opted for cyclo-destructive procedures. This factor, however, does not seem pertinent in the modern era of micro incision vitreous surgery where conjunctival manipulation is minimal.

Iwahashi-Shima *et al*.[5] reported good outcome with filtering surgery in their series. They performed primary trabeculotomy in four cases with open angles and trabeculectomy in one case with closed angles. Two of their cases could be managed with topical treatment alone and one case with peripheral anterior synechiae underwent goniosynechiolysis. However, two of the cases, one that underwent trabeculotomy and the other in which trabeculectomy was performed, required repeat surgery.

We perform a combined surgery (trabeculotomy and trabeculectomy with MMC application) in cases of congenital glaucoma as a routine procedure and have found it to be effective in controlling IOP in our pediatric glaucomas. Here also, we performed the same surgery in four eyes and achieved good postoperative IOP control without the need for additional antiglaucoma drugs. We believe, in these children with advanced glaucoma requiring surgery, a single procedure does not seem to be the best modality for persistently elevated IOP and a combined trabeculectomy with trabeculotomy offers a better chance of success. Mandal *et al*.[15] have previously described the benefits of a combined procedure in congenital glaucoma. Moreover, a successful first-time surgery obviates the need for repeat exposure to general anesthesia with its attendant risks and also ensures sustained IOP control and no further damage to the already compromised ONH.[16] There are no reports on the results of combined surgery in premature

children with ROP; however, we achieved favorable results in our series.

One of the limitations of the study is that we did not perform routine IOP measurements, evaluation of CD, or biometry in all eyes that underwent treatment for ROP. Since the increased CD and ONH changes were used to assess glaucoma, we may have missed those with ocular hypertension and some early cases of glaucoma. This could have led to under-reporting of glaucoma in this cohort. Notably, our study included only those eyes that had undergone a successful vitrectomy with good postoperative outcomes to prevent confounding of data by cases which progress or develop sequelae and might develop variable rates of secondary glaucoma. Therefore, we may have underestimated the true incidence of glaucoma after stage 4 ROP surgery as cases with complicated/unsuccessful vitrectomy were excluded. However, since stage 4 ROP surgery usually has good outcomes, the number of unsuccessful surgeries would be small and this may not be a gross underestimation. Second, as gonioscopy was done only in eyes diagnosed with glaucoma, it becomes difficult to say whether the features of goniodysgenesis were limited only to these cases and to ascertain the true role of goniodysgenesis as a cause for development of glaucoma. Future studies are warranted to add to the current findings.

Conclusion

In conclusion, glaucoma, though occurs less commonly after successful surgery for stage 4 ROP, needs a high level of suspicion for timely detection. We believe it is advisable to perform routine glaucoma evaluation including IOP measurements and ONH evaluation in cases of ROP undergoing surgery so as not to miss them; however, the frequency and duration of the follow-up visits remain open for debate. Surgical intervention with combined trabeculotomy–trabeculectomy with MMC appears to provide good IOP control and may be considered in the management of these cases. The findings of this study could be important in counseling parents of children with ROP that undergo vitreous surgery as to the development, presentation, and management protocols for glaucoma.

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Conflicts of interest

There are no conflicts of interest.

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