Original Article

Surgical outcomes of immediate sequential bilateral vitreoretinal surgery for advancing retinopathy of prematurity

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Purpose: Bilateral eye surgery in the same session may be required for advancing stage 4 retinopathy of prematurity (ROP). The purpose of this study was to evaluate the outcomes of immediate sequential bilateral vitreoretinal surgery (ISBVS) in stage 4 ROP. **Methods:** In a retrospective interventional study at a tertiary care center, 60 eyes of 30 infants who underwent ISBVS for stage 4 ROP between December 2015 and May 2017 were studied. In cases with clear retrolental access, 25G or 27G lens sparing vitrectomy (LSV) was performed and in the rest 25G lensectomy with vitrectomy (LV) was performed through clear corneal entries. The final anatomical outcome measures were the status of tractional retinal detachment (TRD) and macular status. **Results:** The mean gestational age was 28.4 ± 2.0 weeks and birth weight was 1214.5 ± 329.7gms. The mean postconceptional age at surgery was 40.8 ± 2.2 weeks. Stages 4a and 4b were present in 86.7% and 13.3% eyes respectively. LSV was performed in 95% eyes whereas LV was performed in the rest. None of the eyes developed lens touch, choroidal hemorrhage, postoperative hypotony, corneal decompensation, or endophthalmitis. At last follow-up (mean 45 weeks, range 20–68 weeks), macula was attached in 90% eyes with the TRD resolved completely in 61.7% eyes and significantly decreased in another 25% eyes. Sequalae included macular drag, epiretinal membrane, and progression to fibrotic stage 5 disease. **Conclusion:** ISBVS is safe and effective for bilateral stage 4 ROP and should be recommended in rapidly progressive cases.

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Severe progressive bilateral stage 4 retinopathy of prematurity (ROP) needs urgent surgery in both eyes to prevent progression and irreversible blindness.[1] The fellow eye has the risk of poor anatomical and visual outcome if the surgery is performed days/weeks later, following the usual protocol of operating only one eye at a time to avoid the risk of bilateral infection. Since these babies are sick with multiple life-threatening comorbidities, subjecting them to repeated general anesthesia (GA) carries high risk of morbidity and mortality.[2]

Immediate sequential bilateral vitreoretinal surgery (ISBVS) is emerging as a preferred approach to overcome these issues.[3] Timely management of both eyes in a single sitting leads to faster recovery and better anatomical and functional outcomes.[4] This has the advantage of only single exposure to GA for both eyes, which is safer for these small babies.[3,4] Though bilateral simultaneous surgeries pose the risk of bilateral endophthalmitis, ROP is possibly one of the very few pediatric eye diseases where bilateral surgery in same sitting seems justified.

Bilateral ROP surgeries in same session are being performed routinely at many centers, but there is paucity of literature available on the safety and outcomes of ISBVS in ROP. In a multicentric retrospective case series, Yonekawa *et al*. reported ISBVS to be safe and feasible in short term for pediatric patients with bilateral vitreoretinal pathologies.[3] There is no single-center comprehensive study assessing the outcomes of ISBVS in ROP till date. We report our outcomes of ISBVS in a large cohort of premature infants with advancing stage 4 ROP followed over a longer period of time.

Methods

This study was a retrospective review of ROP cases undergoing ISBVS at our center during a period of 18 months (December 2015 to May 2017). The study adhered to the tenets of the Declaration of Helsinki. The parents were counselled preoperatively in detail, emphasizing the need for urgent surgery for progressive blinding disease in both eyes, the benefits of single-session timely surgery avoiding multiple GA sessions, and the rare but possible risk of bilateral infection. A written informed consent explained in detail the possible ocular and systemic risks and complications involved in the procedure under GA.

ISBVS included vitrectomy with or without lensectomy, done in both eyes for stage 4 ROP during a single anesthesia

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session. Stage 5 cases were excluded from the study. All surgeries were performed by a single surgeon.

If tractional retinal detachment (TRD) was limited to posterior or mid-vitreous with nil/minimal retinal lens apposition, and there was enough space to enter into retrolental space, 25G or 27G lens sparing vitrectomy (LSV) was performed; otherwise 25G lensectomy with vitrectomy (LV) was performed through clear corneal entries. Partial fluid–air exchange was done in all cases at the end of surgery, to aid in sutureless wound closure. The corneal incisions were hydrated at the end of surgery. The sclerotomy sites and clear corneal entry wounds were self-sealing in majority of eyes. Rarely in cases of suspected wound leaks, the scleral incisions were sutured with 7/0 polyglactin 910. After completing surgery in one eye, the fellow eye was prepared and the surgical team rescrubbed. A new set of surgical instruments and fluids were used in the fellow eye.

The demographic details, birth history, systemic history, disease classification details, and previous treatment details of ISBVS cases were collected. Preoperative TRD location and height, macular status, and disc status were noted. A note was made of the surgical details such as the route of vitrectomy, intraoperative complications, and the need for gas or silicone oil tamponade. Postoperative outcome measures at the final visit included development of cataract and glaucoma, location and height of residual TRD, posterior pole status, final anatomical outcome and need for re-surgery.

The data entry was performed and analyzed using the statistical package for the social sciences (SPSS) 22.0 software (IBM, New York, US). The qualitative data was expressed as frequency as well as percentages. The Student *t* test was used to compare continuous variables between two groups. Parametric data was subjected to one-way Analysis of Variance (ANOVA) or Kruskal–Wallis test for comparison between more than two groups. Groups having nonparametric or categorical data were subjected to Pearson Chi-square test or Fischer's exact test for comparison between the groups. Chi-square test was used if the cell value was ≥5 in all the cells of the contingency table. If any cell had value <5, then Fischer's exact test was used. Freeman–Halton extension of Fischer's exact test was used for analysis in larger than 2*2 contingency tables with any cell value <5. A *P* value ≤0.05 was considered statistically significant.

Results

Baseline characteristics

Sixty eyes of 30 babies underwent ISBVS during the study period. The mean gestational age was 28.4 ± 2.0 weeks (26–32 weeks) and the mean birth weight was 1214.5 ± 329.7gms (750–1800 gms). Males constituted 56.6% (17/30) of the babies.

Nineteen eyes (31.7%) had disease in zone I while rest 41 (68.3%) had zone II disease. Aggressive posterior ROP (APROP) was readily noted in 12 eyes (20%); 10 eyes in zone I and 2 eyes in zone II. APROP was difficult to ascertain in other nine zone I eyes due to the presence of TRD.

Stages 4a and 4b were present in 86.7% (52/60) and 13.3% (8/60) eyes respectively. Four babies (13.3%) had asymmetric disease with stage 4a in one eye and stage 4b in the fellow eye. All 12 APROP eyes had stage 4a disease at presentation. TRD was annular or circumferential in 30% (18/60) eyes. Predominant involvement of nasal and temporal quadrant was seen in 25% (15/60) and 23.3% (14/60) eyes respectively. The rest of the eyes (*n* = 13) had a predominant or equal involvement of the other quadrants as well. The extent of TRD was 8.4 ± 3.4 clock hours (range 3 to 12 clock hours). Majority of the eyes (50/60) had received some treatment prior to presentation to us (laser photocoagulation = 44, anti-VEGF injection = 2, or both = 4).

Intraoperative parameters

Mean postconceptional age at surgery was 40.8 ± 2.2 weeks (37–45 weeks). 25G and 27G LSV were performed in 88.3% (53/60) and 6.7% eyes (4/60) respectively; while in the rest 25G clear corneal LV was performed (two and one eye with stage 4a and 4b disease respectively). 27G LSV was performed in selected cases with low TRD height where minimal peripheral manipulation was needed. None of the eyes developed complications like corneal haze, epithelial defect, inadvertent lens touch, cataract, vitreous hemorrhage, retinal break, and subretinal hemorrhage. None of the eyes required gas or silicone oil tamponade. While four eyes required scleral wound closure with 7/0 polyglactin 910 suture, none of the eyes with corneal incisions needed sutures for closure.

Postoperative outcomes

The mean duration of follow up after surgery was 45 weeks (20–68 weeks). All eyes had excellent wound closure; shallow anterior chamber, hypotony, and choroidal detachment were not seen in the early postoperative period. None of the eyes developed corneal decompensation, cataract, and endophthalmitis on follow up. One infant had a cup-disc ratio 0.7:1 OU, and was then detected with high intraocular pressure (IOP) measurements, which was subsequently controlled on topical antiglaucoma medication. Vitreous hemorrhage occurred in four eyes of two infants (operated with 27G system) and required vitreous lavage in one eye. Macular epiretinal membranes were noted in four eyes.

TRD resolved completely in 61.7% eyes (37/60) and decreased significantly in height with minimal residual tractional remnants in 25% eyes (15/60) at last follow-up. TRD worsened in 8.3% eyes (5/60) with eventually closed-funnel fibrotic stage 5 disease developing in four of them. Macula was attached in 90% eyes (54/60) at the last follow-up, out of which 27.8% eyes (15/54) had macular drag (temporal/nasal: 10/5). In eyes with APROP (n = 12), TRD resolution and significant decrease in TRD was noted in eight and three eyes respectively, with macular attachment noted in all eyes at last follow-up.

The extent and location of TRD at baseline did affect the final status of TRD significantly (Student *t* test, *P* = 0.003 and Fischer's exact test, *P* = 0.002, respectively). The extent of TRD at baseline was less in the eyes which had improvement (resolution/significant decrease) in TRD (7.9 ± 3.4 clock hours) as compared to those eyes in which it remained stable or worsened (11.6 ± 1.0 clock hours). Majority of the eyes with predominant temporal/nasal involvement at baseline had resolution or significant decrease in TRD (n = 29/30) while annular TRD remained the same or worsened (n = 7/18).

Re-surgery was required only in one eye for vitreous hemorrhage. The surgical outcomes as per different stages of disease are shown in Table 1. Fellow eyes did not differ significantly in any baseline characteristics as well as postoperative outcomes [Table 2].

Table 1: Surgical characteristics and outcomes of bilateral ROP surgery

Stage of disease	4A	4B	Total
Number of eyes *n* (%)	52 (86.7%)	8 (13.3%)	60 (100%)
Baseline characteristics			
Zone of disease			
Zone I	19	0	19 (31.7%)
Zone II	33	8	41 (68.3%)
Previous treatment			
Laser	39	5	44 (73.3%)
Anti-VEGF* injection	2	0	2 (3.3%)
Laser + Anti-VEGF*	3	1	4 (6.6%)
Baseline TRD†			
Annular	14	4	18 (30%)
Predominantly temporal	13	1	14 (23.3%)
Predominantly nasal	13	2	15 (25%)
Others	12	1	13 (21.7%)
Surgery performed			
LSV‡	50	7	57 (95%)
LV§	2	1	3 (5%)
Outcomes			
TRD†			
Resolution	37	-	37 (61.7%)
Significant decrease	12	3	15 (25%)
No change/stable	1	2	3 (5%)
Increase/worse	2	3	5 (8.3%)
Macular status			
Macula attached	51	3	54 (90%)
Macular drag	13	2	15 (25%)

*VEGF=Vascular endothelial growth factor, †TRD=Tractional retinal detachment, ‡LSV=Lens sparing vitrectomy, §LV=Lensectomy with vitrectomy

Table 2: Comparison of baseline parameters and outcome between the fellow eyes

Parameter	Right eye	Left eye	*P* (statistical test)
Zone			
Zone I	9	10	0.78 (Chi
Zone II	21	20	square test)
Stage			
Stage 4a	26	26	1 (Fischer's
Stage 4b	4	4	exact)
TRD* location			
Annular	10	8	0.76 (Chi
Nasal/temporal	14	16	square test)
TRD extent (clock hours)	8±3.7	8.7±3.2	0.44 (Student *t*)
Final TRD status			
Regressed/decreased	25	27	0.70 (Fischer's
Stable/worse	5	3	exact)
Final macular status			
Attached	21	18	0.32 (Fischer's
Attached but dragged	5	10	exact)
Detached	4	2	

*TRD=Tractional retinal detachment

Prognostic factors for macular outcomes

Univariate analysis of the effect of baseline disease characteristics on final macular status was performed [Table 3]. Stage and extent/location of TRD had a significant effect on final macular outcome. Almost all stage 4a eyes (51/52, 98.1%) had attached macula at final visit with normal macular morphology in 73% eyes (n = 38/52) and macular drag in 25% (13/52) eyes. In stage 4b cases, macular attachment was noted in only 37.5% (3/8) eyes out of which 2 eyes had macular drag and only one had normal macular morphology. Nearly all eyes with predominantly temporal (13/14) or nasal TRD (15/15) had final macular attachment, while in annular TRD only 72.2% eyes (13/18) achieved macular attachment. Gestational age, sex, birth weight, postconceptional age, and previous treatment did not have a significant bearing on final macular status. Although in treatment-naive eyes, 80% (8/10) achieved macular attachment while 92% (46/50) of previously treated eyes achieved macular attachment; this difference was not statistically significant [Table 3]. The predictors of macular outcome, that is, the stage of disease and the TRD extent were compared in between the groups with normal macula and macular drag at follow-up (subgroup analysis) and no statistical difference was observed (Fischer's exact $P = 0.12$ and Kruskal-Wallis test $P = 0.18$, respectively, see [Table 3]).

Discussion

Retinopathy of prematurity (ROP) is a blinding disease in low birth weight preterm babies.[1] Delayed surgery may lead to dismal surgical outcomes in severe bilateral progressive advanced ROP.[1] If single eye surgery is performed at a time, the fellow eye is at risk of becoming worse with poor anatomical and visual outcomes. Also, these preterm infants may have multiple systemic comorbidities. The risk of GA-related mortality in pediatric population is estimated to be as high as 1 in 10,000 children and in preterm infants it is even higher.[5] Premature infants may undergo cardiorespiratory compromise during the perioperative period.[6] As both induction and extubation are the high-risk phases of anesthesia, the risk is greater for infants undergoing more than one sitting for bilateral disease.

ISBVS is a term suggested for vitreoretinal surgery performed in both eyes during the same anesthesia session.[3] In delayed bilateral vitreoretinal surgery, the second eye is operated days to weeks later requiring an additional anesthesia session. ISBVS carries the advantage of only one exposure to anesthesia for both the eyes.[3,4] Also, timely management of both the eyes may lead to better anatomical and functional outcomes. Immediate sequential bilateral cataract surgery (ISBCS) has been performed for several years but as an elective surgery,[7-9] which is of shorter duration with relatively older babies and thus carries less risk of anesthesia-related morbidity and mortality.

Risk of possible endophthalmitis warrants a check on such bilateral surgeries. Endophthalmitis after vitrectomy for ROP has not been reported previously. Risk of endophthalmitis after pars plana vitrectomy (PPV) is 0.03%–0.08%.[10] Risk of bilateral postoperative endophthalmitis after PPV is estimated to be much lesser around 0.0009%–0.0064%.[3] Bilateral intravitreal anti-VEGF injections have been performed worldwide and carry near similar rates of endophthalmitis as in intraocular surgeries.[11] The ethical issues are limited in ROP as there are undoubtedly major advantages of performing this vision-saving surgical intervention in a very selected group of rapidly progressive blinding ROP in preterm babies, while minimizing GA morbidity and taking extra precautions to

Table 3: Effect of the baseline disease characteristics on the macular status after vitrectomy

Parameter	Macula attached (*n*=39)	Macula attached and dragged (*n*=15)	Macula detached (*n*=6)	*P* (Statistical test)
Gestational age (week, mean SD)	28.4±2.1	28.2±2.4	29.3±2.1	0.55 (Kruskal-Wallis)
Birth weight (gram, mean SD)	1214±349	1187±303	1283±299	0.81 (Kruskal-Wallis)
PCA* (week, mean SD)	41.0±2.2	40.8±2.5	39.5±2.1	0.29 (Kruskal-Wallis)
Sex				
Male	24	9	1	0.15 (Fischer's exact)
Female	15	6	5	
Previous treatment				
Yes	35	11	4	0.14 (Fischer's exact)
No	4	4	2	
Zone				
Zone I	15	4	0	0.20 (Fischer's exact)
Zone II	24	11	6	
Stage				
4a	38	13	1	<0.0001‡ (Fischer's exact)
4b	1	2	5	
Eye				
Right	21	5	4	0.32 (Fischer's exact)
Left	18	10	2	
TRD† extent (clock hours, mean SD)	7.5±3.7	9.4±2.5	11.5±1.2	0.013§ (Kruskal-Wallis)
TRD location				
Annular	10	3	5	0.09‖ (Fischer's exact)
Nasal/Temporal	20	9	1	
Others	9	3	0	

*PCA Postconceptional age, †TRD Tractional retinal detachment. ‡Comparison by group (*P*=0.12 between 1 and 2, *P*<0.0001 between 1 and 3, *P*=0.002 between 2 and 3). §Comparison by group (*P*=0.18 between 1 and 2, *P*=0.008 between 1 and 3, *P*=0.18 between 2 and 3). ‖When comparing annular vs nasal/temporal group in terms of final macular status (normal/drag/detached), *P*=0.048. When comparing annular vs nasal/temporal group in terms of macular attachment (attached/detached), *P*=0.022

minimize infection and providing dedicated postoperative monitoring support.

Shah P K *et al*. studied the safety and efficacy of simultaneous bilateral 25 G LSV for active stage 4 ROP in 20 eyes of 10 babies and followed up for 4–17 months.[4] The mean birth weight was 1265gm and the gestational age was 29.8 weeks. The mean postconceptional age at surgery was 38.5 weeks. Anatomic success rate for stage 4A was 100% and stage 4B was 89%. No cases developed postoperative infection, though 15% eyes (3/20) developed glaucoma requiring medication on follow-up. Only one eye developed lens touch requiring lensectomy intraoperatively. They concluded that simultaneous bilateral 25 G LSV for stage 4 ROP was safe. However, this study was limited by a smaller cohort. Also, baseline TRD characteristics were not evaluated with postoperative outcomes.

Yonekawa *et al*. did a multicentric retrospective study on ISBVS conducted in 24 centers worldwide with 344 surgeries in 174 pediatric patients (344 eyes).[3] ISBVS was performed in 250 eyes of 120 ROP infants (mean gestational age of 26.3 weeks; birth weight of 930.1 gm) at postconceptional age of 41.5 weeks. Majority of vitrectomies (66.9%) were performed with 23 gauge instruments. There were no intraoperative complications like endophthalmitis, hypotony, or choroidal hemorrhage. Also, no anesthesia-related death, malignant hyperthermia, anaphylaxis or cardiac event occurred. Anatomical success was achieved in 89.8% eyes. However, grouped outcomes in various stages were not analyzed and postoperative evaluation was done till one month only.

Our study was a single center study with a large cohort of ROP infants operated by a single surgeon, thereby removing surgeon-related bias. Infants in our study were more premature and operated at a later postconceptional age (depending on presentation) as compared to the study by Shah PK *et al*.[4] This may be responsible for advanced disease and lesser attachment rates in stage 4b ROP cases in our study.

Eyes with advanced disease (stage 4b) had poor surgical outcomes as compared to early disease (stage 4a). Most eyes with advanced disease had persistent or worse TRD following surgery. While early cases had near normal macular features eventually (73%), advanced cases had macular drag (2/3 eyes) in the postoperative period. This highlights the importance of immediate surgical intervention in stage 4a disease to prevent rapid advancement to stage 4b or stage 5 ROP.

Preoperative laser or bevacizumab injection have been previously found to improve the final anatomical outcomes by Xu Y *et al*.[12] Previous treatment may limit the progression to more advanced stages of ROP and also limit the extent of TRD. This in turn may affect the formation of macular drag and ectopia. Though previous treatment did not significantly affect final outcome in our study, our numbers were small to conclusively comment on this.

Preoperative TRD extent as well as the location remained key prognostic factors for TRD resolution and macular attachment in our study. The presence of annular TRD was a poor prognostic factor as compared to TRD involving nasal and temporal quadrants in stage 4b disease. Contrary to this,

Bhende *et al*. had previously reported that localization of TRD does not affect the anatomical outcomes.[13] We believe that annular TRD may be an advanced morphological form of vascular stage 4a disease and needs to be addressed as early as possible.

Involution sequalae in the form of macular ectopia and dragging of retina over the disc was a concern in a few eyes. The predominant quadrant involved in TRD decided the direction of drag, with temporal drag twice as common as nasal drag. The zone and stage of disease did not affect macular drag formation. We believe perhaps the height of TRD may affect this phenomenon.

Previously known APROP eyes fared similar to other eyes unexpectedly. None of these eyes worsened following surgery and mostly had macular attachment at last follow-up. We believe that as most of these babies were on close follow-up, TRD was detected and operated early.

Many surgeons are still hesitant to perform bilateral surgeries in this rapidly progressive disease due to ethical concerns, risk of bilateral endophthalmitis, prolonged GA exposure, and the need for an experienced anesthesia team with dedicated neonatal intensive care unit support. Although bilateral simultaneous intravitreal injection has been reported to be as safe as sequential injection,[11] postoperative endophthalmitis may still pose a serious medico-legal concern for the surgeon. But the safety margin is highly increased if the second eye is treated as an independent surgery with added precautions like replacing infusion fluids, surgical instruments, vitrectomy set, and rescrubbing by the whole surgical team. Nevertheless, a detailed parent counselling and informed consent is helpful in case of adverse events. The additional GA time-associated morbidity is of less concern as these are short-duration surgeries. GA has been implicated to be a risk factor for neurodevelopmental impairment and death in very low birth infants, but this remains unproven by randomized control trials.[14] Although the chance of occurrence of cardiovascular complications in premature infants may increase with the duration of GA, there are no prospective studies comparing the effect of duration of GA on the health of premature babies.

The focus of this study was the intraoperative and postoperative safety and outcomes of bilateral simultaneous vitrectomy, but it had some limitations. Since it was a retrospective review, anesthesia-related factors and total surgical time were not evaluated. The visual outcome could not be assessed in such young infants and IOP was not measured routinely which could have missed out on ocular hypertension cases and those with early glaucomatous disc damage. The study was underpowered to assess the endophthalmitis risk after bilateral vitrectomy.

Conclusion

ISBVS should be recommended for infants with rapidly progressive bilateral stage 4 ROP who are already at risk for anesthesia-related morbidity and mortality. ISBVS requires strict sterile precautions at all steps of surgery with special emphasis on rescrubbing by OT staff and use of new set of instruments for the second eye. Parents need to be counselled regarding risks of bilateral endophthalmitis and detailed consent should be obtained. Prospective studies are further required to evaluate the long-term outcomes of ISBVS in a larger cohort of ROP infants.

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Conflicts of interest

There are no conflicts of interest.

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