Original Article

Management of Retinopathy of Prematurity: Quest for the Best

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Abstract

Purpose: *We analysed the effect of primary laser ablation and primary intravitreal ranibizumab (IVR) therapy administered alone or followed by peripheral laser ablation for the treatment of type I ROP and Aggressive Posterior ROP (APROP).*

Methods: *Sixty eight eyes of 35 babies treated for ROP were analysed from September 2016 to March 2019. 14 eyes of seven babies underwent primary laser treatment. Primary IVR was given in 54 eyes of 28 babies.*

Results: *Nine of 14 (64.28%) eyes recovered with laser treatment and five progressed to stage IV or V ROP which did not recover even with surgical intervention. 44 of 54 (81.48%) eyes recovered fully after single dose of IVR by ten weeks and remaining ten eyes underwent laser of the avascular area after two to ten weeks following IVR therapy. Six of these ten eyes recovered fully while four progressed and underwent surgery for stage IV or V. Three of these four operated cases had attached retina after surgery. Hence 50 of 54 eyes (92.59 %) eyes who underwent primary IVR therapy or with subsequent laser recovered while only four of the nine eyes (64.28 %) recovered with primary laser treatment. No progression, reactivation and systemic complications were observed over an average follow-up of six months in babies who received primary IVR alone or with subsequent management.*

Conclusions: *IVR or IVR followed by laser by ten weeks following injection is a safe and efficacious primary treatment for ROP with gratifying results in type I disease or APROP.*

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Keywords: *Intravitreal ranibizumab for Retinopathy of prematurity, IVR followed by laser for ROP.*

Introduction

The role of vascular endothelial growth factor (VEGF) in the pathogenesis of ROP has been described. Many recent reports of anti-VEGF use in ROP demonstrated that it can be a safe and effective treatment.[1,2,3,4] Along with these, reports about reactivation and retinal detachment after injection are also not rare.[3,4] Anti-VEGF treatment promotes rapid regression of acute-phase of ROP (neovascularisation and plus disease), allows potential for retinal vascularization, approaches eyes with a rigid pupil and minimizes stress of laser to the baby. These potential benefits over conventional laser photocoagulation are a reason for their growing popularity in the management of ROP. These agents come with a few limitations which also include long term possible cardiovascular or any other systemic complications. Our series of 68 eyes of 35 babies with ROP is large of its kind in northern India highlighting the role of systematic intravitreal ranibizumab (IVR) and IVR with subsequent laser by ten weeks in the management of this preventable cause for childhood blindness.

Material and Methods

Sixty eight eyes of 35 babies referred from neonatology unit of our hospital were screened for ROP and were included in this prospective interventional study over a period of two years and six months from September 2016 to March 2019. Gestational age at birth, birth weight (in grams), corrected gestational age at first intervention, single or multiple gestation in the mother at delivery, mode of delivery (vaginal/caesarean), situation of the amniotic fluid (oligohydramnios/polyhydramnios), post-natal events in the form of intraventricular haemorrhage, necrotising enterocolitis, neonatal hyperbilirubinemia, bronchopulmonary dysplasia, blood transfusions and the need for oxygenation and intubation were analysed from the paediatric records and were tabulated. Complete antenatal history and birth history was taken. Stage and zone of ROP involvement was documented at every visit and the screening protocol was followed as per standard operating procedures as given by National neonatology forum (NNF) clinical practice guidelines, India. Babies with any major congenital ocular anomalies, other retinal disorders, congenital cardiovascular anomalies, loss to follow up, refusal of parent consent or death during follow-up were excluded from the study. Eyes of patients fulfilling the inclusion criteria were selected and intervened after obtaining a written informed consent from the parents after explaining the nature of the disease and the need for the available treatment modality at that particular time. The study was approved by the ethics committee of the institution. At each visit, complete ophthalmic examination was done including iris status for presence or absence of neovascularisation and the status of the lens. Indirect ophthalmoscopy was done at every visit after dilatation of the pupil with tropicamide (0.4%) and phenylephrine (2.5%). A sterile paediatric eye speculum and scleral indenter was used for every baby. In the initial part of the study, 14 eyes of seven babies who needed treatment primarily received laser (Green laser, Visulas 532s) photocoagulation using laser indirect ophthalmoscope. IVR was approved for the treatment of ROP by Drug controller General of India

(DCGI), 11th Subject Expert Committee (SEC) Ophthalmology meeting in June, 2015. Henceforth it was introduced in the treatment of ROP at this institute. In the quest for better results, next 54 eyes received IVR. 25mg/0.025 ml of IVR was administered following all aseptic precautions inside the operation theatre after written informed consent from both the parents. Wherever indicated both eyes were injected at an interval of four to eight days. 44 of 54 eyes recovered with monotherapy with IVR by ten weeks post IVR injection. Recovery was considered fully vascular zone II, no stage of ROP or plus disease. Ten of 54 eyes were lasered after IVR injection when progression of the disease was noticed or at ten weeks if they had avascular area in zone II, any stage of ROP or plus disease. Prior to laser treatment, these ten eyes had involvement of zone 1 with stage II in one eye and stage III and III+ in two eyes; Zone II involvement with stage II with plus disease in one eye, stage III and stage III with plus disease in one eye each; APROP was seen in two eyes. Lens sparing pars plana vitrectomy (LSV) was performed in four eyes on observing progression to stage IV or V after laser or IVR with and without laser. These eyes which underwent LSV had zone 1 with stage II and stage III in one eye each and APROP in two eyes prior to IVR.

Results

Table 1 elucidates the demographic profile of the babies with the risk factors. Table 2 elucidates the severity of ROP and the effect of the two modalities of treatment on ROP. Following laser, nine of 14 (64.28%) eyes recovered (Table 2), four of 14 eyes (28.57%) progressed to stage IV and I eye progressed to stage V. All these five eyes were operated subsequently without any recovery and the retina remained detached. Following IVR injection, 44 of 54 (81.48%) eyes recovered by ten weeks post IVR and had no recurrence at an average follow-up period of 6.24 ± 1.02 months (Table 2). 10 eyes of these 54 eyes were subsequently lasered on follow-up two to ten weeks post IVR injection after observing progression, avascularity of peripheral retina in zone II, any stage of ROP or plus disease. Six of these ten eyes which were lasered recovered (Table 2) and the remaining 4 underwent lens sparing pars plana vitrectomy under general anesthesia in view of progression to stage IV. Three of four eyes recovered. One patient was lost to follow-up and hence cannot be commented.

Table 1: Demographic profile of the babies with ROP

	LASER (n=14 eyes of 7 babies)	**IV RANIBIZUMAB (n=54 eyes of 28 babies)**
Gestational age at birth (weeks + days)	28.42 ± 1.78 weeks + 2.85 ± 1.87 days	28.75 ± 1.50 weeks + 2.53 ± 1.80 days
Males/females	4/3	16/12
Birth weight (grams)	1185.07 ± 247.36	1117.51 ± 215.14
Corrected gestational age at first intervention	35.07 ± 1.43 weeks + 4.64 ± 1.86 days	34.87 ± 1.66 weeks + 3.26 ± 1.73 days
Single/Twins	4/3	16/12
Natural birth/ Caesarean section	4/3	17/11
Sepsis (n)	5	16
Intraventricular hemorrhage (n)	1	1
Necrotizing enterocolitis (n)	1	1
Oxygenation & Intubation (n)	4	9
Neonatal hyperbilirubinemia	3	3
Bronchopulmonary dysplasia	0	3
HS-PDA	2	0
Blood transfusions	2	6
Average follow up duration (months)	6.5 ± 2.31	± 1.02

Table 2: Profile of ROP in eyes and effect of various modalities of treatment on different stages of ROP

	LASER (n=14 eyes of 7 babies)	**IV RANIBIZUMAB (n=54 eyes of 28 babies)**
ZONE 1 ROP (Eyes)	6	32
ZONE 2 ROP (Eyes)	6	16
APROP (Eyes)	2	6
Zone and stage before treatment	**Zone 1** S IV 1 S II+ 3 S III 2 **Zone 2** S III+ 1 S III 3 S III+ 1 S IV 1 APROP 2	**Zone 1** S I+ 3 †, ‡ S II 1 S II+ 14 †, ‡ S III 4 † S III+ 10 **Zone 2** † S II+ 10 † S III 1 † S III+ 5 †, ‡ APROP 6
Recovered with primary treatment	9 eyes	44 eyes 50 eyes after laser following IVR (Two to ten weeks post IVR)
Pars plana vitrectomy (PPV) surgery	5 Recovered after PPV surgery-1 No recovery- 4	4 (operated after IVR followed by laser) Recovered after surgery-3 Loss to Follow-up (FU)-1
Follow up of APROP	Recovered-1 Did not recover-1	Recovered- 5, Loss to FU-1(cannot comment)

**S- stage, + - plus disease*
†- Zone and Stage in eyes which needed laser post IVR
‡- Zone and Stage in eyes which needed surgery

Discussion

Laser photocoagulation has been the gold standard of treatment for ROP. Multiple studies have confirmed its safety and efficacy in type I ROP with satisfactory structural and refractive outcomes.[5,6,7] Pharmacologic therapy is ushering a new era of ROP management. BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) trial by Mintz-Hittner, H.A et al suggested that bevacizumab was effective in treating ROP and was

more effective than laser treatment in zone I ROP cases.[1] It demonstrated increased efficacy of intravitreal bevacizumab as compared with conventional laser therapy for stage III plus retinopathy of prematurity when both zones I and II were considered.[1] Various studies have concluded bevacizumab as effective and well tolerated agent in cases of ROP especially in stage III and in severe and posterior ROP with satisfactory anatomical outcome.[8,9,10] BEAT ROP study is nearly ten years old. However no long term systemic complications have been reported in these cases till date. The results of BEAT ROP study highlight that a careful follow-up is warranted in infants who were treated with intravitreal bevacizumab monotherapy as four of 70 babies (6%) developed recurrence[1] Ranibizumab is a humanized recombinant G1 kappa isotype antibody fragment. It is structurally derived from the light chains of bevacizumab and has approximately ten times greater affinity for VEGF. Serum VEGF levels decrease after bilateral injection of 0.2 mg of ranibizumab, reaching a lowest at approximately two weeks and returning to normal levels four weeks after injection (Bakri SJ 2007).[11] In 2016, Mari Jeeva Sankar et al evaluated the efficacy and safety of administration, or both, of anti-VEGF agents compared with conventional therapy in premature infants with ROP.[12] They observed that intravitreal bevacizumab reduces the risk of refractive errors during childhood when used alone. Intravitreal pegaptanib reduces the risk of retinal detachment when used with laser therapy in infants with type I ROP.[12] Table 3 enlists various studies conducted on IVR and IVR with subsequent laser and their conclusions.

Our case series of 68 eyes of 35 babies is the first systematic study in a tertiary care center in northern India. The authors evolved in the management of ROP from laser photocoagulation to IVR as a primary management modality for disease involving zone I, zone II posterior and APROP. Recovery was seen in 64.28% (Nine of 14) babies who underwent primary laser treatment. Laser photocoagulation had increased the chances of progression to stage V and decreased the surgical success rate in these cases. Recovery was seen in 81.48 % (44 of 54) eyes in our study who received primary IVR. By ten weeks ten eyes were lasered post IVR injection. Seven of these ten eyes had progression of the disease and were lasered earlier. Three eyes which had avascularity of the peripheral retina involving zone II, with any stage of ROP or plus disease were lasered at 10 weeks. 50 of 54 eyes recovered with IVR or IVR with subsequent laser which was done by ten weeks post IVR. Of these four eyes were subsequently operated of which three recovered and one baby was lost to follow-up (FU) and cannot be commented. Although the percentage of

Table 3: Table enlisting various studies conducted on IVR and IVR with subsequent laser and their conclusions.

STUDIES ON INTRAVITREAL RANIBIZUMAB (IVR)	CONCLUSIONS
Castellanos MA et al in July 2013 evaluated the ocular outcome in premature infants treated with IVR injection for ROP over a period of three years where six eyes were included.[13]	Complete resolution of neovascularisation was observed after single injection of IVR with no demonstrable ocular or systemic adverse effects over three years of follow up.
In a study conducted by Baumal CR et al in 2015, eight eyes of four infants received primary ranibizumab (0.2 mg) treatment.[14]	Intravitreal ranibizumab induced rapid, complete regression of high-risk posterior ROP with continued retina growth peripherally. Recurrence of ROP in posterior zone seen at eight to 11 weeks may be managed with subsequent laser as IVR spares the posterior retina for laser.
Gunay M in 2017 evaluated the efficacies and treatment outcomes following intravitreal bevacizumab (IVB), IVR, and laser photocoagulation (LPC) in 134 infants (264 eyes) with ROP. There were 55 infants in the IVB group, 22 infants in the IVR group, and 57 infants in the LPC group.[15]	Both IVB and IVR treated infants had significantly better refractive outcomes in Zone I ROP as compared to LPC treated infants at one year and six months of adjusted age. Disease recurrence rate was higher with IVR at 62.90 ± 8.61 weeks unlike IVB at 69.18 weeks ± 17.25 weeks.
Zhang G in 2017 compared the efficacy of IVR monotherapy and laser therapy for treatment-requiring retinopathy of prematurity (ROP) in Zone II in 100 eyes of which 50 eyes of 25 infants received IVR and 50 eyes of 25 infants underwent laser photocoagulation.[16]	Concluded that IVR appears to regress ROP and continues to promote the vascularization of peripheral retinal vessels. However a substantial proportion of infants (13 of 25 infants) developed recurrence after IVR monotherapy at 49.94 ± 14.67 weeks at last follow-up. IVR was not recommended as a single-dose monotherapy for Zone II treatment-requiring ROP.
Feng J et al reported the use of intravitreal injection of ranibizumab (IVR, 0.25 mg/0.025 ml) as first-line therapy in a total of 629 eyes of 331 premature infants (206 male and125 female) in China. Laser therapy and other treatments were used as supplemental treatments when required. All treated infants received at least 6 months of follow-up.[17]	245 eyes (39.0%) demonstrated recurrence with the reappearance of neovascularization and the return of plus disease, which required further treatment. The mean time to recurrence was 8.57 ± 3.73 weeks and occurred as early as four weeks or as late as 29 weeks. The rate of recurrence with type 1 prethreshold ROP in their study was15.9% (18 of 113 eyes), 38.2% (157 of 411 eyes) with threshold ROP, and 66.7% (70 of 105 eyes) with APROP and showed a statistically significant increase with increasing stage (P<0.001 for all). The recurrence rate was higher in zone I ROP (61.6%) than in zone II ROP (31.0%; P<0.001). The additional treatments included a second IVR treatment (92 eyes; 37.6%), supplemental laser therapy (146 eyes; 59.6%), external scleral buckle (2 eyes; 0.8%), and vitrectomy (5 eyes; 2.0%). Thirty-six eyes underwent a third treatment.
Qinrui Hu et al conducted a retrospective, nonrandomized and noncontrolled study in 2017 to determine the prevalence and risk factors for the recurrence of ROP in Zone II Stage 3+ after ranibizumab treatment. Zone I and APROP cases were excluded. Forty-two patients were included, and 80 eyes with Zone II Stage 3+ were subjected to IVR treatment.[18]	Eleven of 42 patients (26.2%, 18 eyes) had a recurrence of ROP after the initial treatment. The recurrence rate of ROP in Zone II Stage 3+ after initial ranibizumab treatment was notable and preretinal hemorrhage before treatment was associated with the recurrence of ROP in this study.

babies who recovered with IVR alone was more than those who had resolution with primary laser treatment for ROP, the difference could not be evaluated statistically as the number of children included in the two groups was grossly different. 92.59 % (50 of 54) babies presenting with Type I ROP and APROP who underwent IVR alone or followed with laser by ten weeks post IVR injection recovered without surgery (Table 2). IVR not only limits the progression of ROP but also makes it amicable to improvement in case subsequent surgical treatment is required. Surgical outcome is better in neonates treated with IVR as compared to those who underwent laser primarily. No systemic complications were seen in these babies in either group. The earlier studies showing recurrences or progression after IVR monotherapy can then be limited by laser of the eyes which have not regressed by ten weeks post IVR injection. In developing country long follow-up of these babies who are not fully vascularized post IVR injection is difficult as there would be failure to comply with the visits. It is safe strategy to laser the avascular area in zone II as by ten weeks the vessels would have progressed more anteriorly and balance can then be hit by now lasering only the peripheral avascular retina. This results in better outcome. To sum up, laser of avascular area in zone II or presence of any stage of ROP or plus disease by ten weeks post IVR has following advantages:

1. No long follow-up visit required which if missed could be critical to the eyes.
2. Only peripheral avascular retina to be lasered.
3. Babies are still amenable to laser without sedation or general anesthesia

This period is the time when the baby has to follow up in well baby clinic of the hospital for its various vaccinations which are being administered and hence reasonable follow-up is established. The study was limited by the fact that the number of babies included in the two groups was different therefore statistical comparison could not be well established.

Conclusion

IVR with or without subsequent laser by ten weeks of IVR may be considered as a safe and effective treatment option in the management of ROP especially in zone I, posterior zone II disease and also in APROP with gratifying results.

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