Original Research Paper

Volume - 14 | Issue - 08 | August - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Ophthalomology

# BEVACIZUMAB VERSUS LASER THERAPY IN NEONATES WITH RETINOPATHY OF PREMATURITY: A ONE-YEAR INTERVENTIONAL STUDY

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**ABSTRACT** This one-year randomized open-label parallel-group prospective interventional study aimed to study and compare the outcomes of intravitreal injection Bevacizumab 0.625mg versus Nd: YAG laser therapy for the treatment of premature babies with ROP. During one year of study, 338 babies with birth weight ≤ 2000 grams and gestational age (GA) ≤ 35 weeks were screened for ROP at a tertiary ophthalmic center in North India. Out of 338 babies, 157 babies developed ROP. The incidence of ROP among the study population screened was 46.44%. Finally, 120 eyes of 60 babies with ROP, who required treatment, were included in the study and were randomly allocated into two equally distributed groups. Group A comprised infants who received intravitreal Bevacizumab injections (0.625 mg intravitreally), while Group B consisted of infants treated with laser therapy using a frequency-doubled Nd: YAG laser. Retreatment was needed significantly more in Group A (53.33%, 32 eyes) than in Group B (18.33%, 11 eyes) (p=0.02). The mean duration between primary treatment and retreatment was not significant, but disease regression within 1-3 months was notably higher in Group B. Complete regression occurred in 49/60 eyes in Group A and 58/60 in Group B, with 11 eyes in Group A and 2 in Group B showing no regression. The study concludes that both treatments are effective, but laser therapy is more effective, with fewer retreatments and failures. Bevacizumab (0.625mg) is particularly beneficial in reducing severity in aggressive ROP (AROP) when used as a primary treatment.

**KEYWORDS :** Retinopathy of prematurity, treatment, Laser photocoagulation, Intravitreal injection Bevacizumab

## INTRODUCTION

ROP is a significant cause of preventable childhood blindness worldwide.[1] This vasoproliferative disorder which threatens vision, affects the retina of premature infants. Its incidence has been on the rise due to the improved survival rates of infants born at very early GA, with the advancements in neonatal care and resuscitation techniques, especially in middle-income countries like India. The incidence and prevalence of ROP in India have been reported to range between 38%-47%[2].

The principle of ROP treatment involves ablation of the peripheral avascular retina thereby abolishing the hypoxic drive of the retina (mediated by over-expression of VEGF). This results in regression of established ROP.[3] Over the past few decades, laser photocoagulation has often been employed to treat ROP[4]. Treatment can be carried out using a portable infrared diode laser (810 nm), frequency-doubled Nd: YAG laser (532nm), or an argon green laser (514 nm) with a laser indirect ophthalmoscope (LIO) delivery system and a 20D or 28D lens. The avascular retina starting from the ridge to the ora serrata, should be ablated in a near-confluent pattern.[5]

Recently, Intravitreal Anti-VEGF agents, such as bevacizumab, have been employed both for monotherapy and in combination with other conventional treatments such as laser therapy or vitrectomy for stages 3+, 4, and 5 ROP.[6] VEGF has a crucial role in both the ischemic and vasoproliferative phases of ROP. The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) trial indicated that bevacizumab had better outcomes compared to laser therapy for zone 1 disease but showed no significant difference for infants with zone 2 disease.[7] It is important to note that recurrences can occur several months after bevacizumab injection, highlighting the necessity for long-term follow-ups.[7]

The objective of this study is to compare the outcomes of injection Bevacizumab (0.625mg) versus Nd:YAG laser therapy for the treatment of premature babies with ROP at a tertiary ophthalmic center in North India.

## MATERIALS AND METHODS

Following approval from the institutional ethical committee, a one year randomized open-label parallel group prospective interventional study was conducted at a tertiary ophthalmic center in North India. The study included newborns with a birth weight of ≤2000 grams and a GA of ≤35 weeks with ROP and required treatment, who were either admitted to the Neonatal Intensive Care Unit (NICU) or attended the outpatient department (OPD). Informed written consent was obtained from all the parents of the neonates participating in the study in their vernacular language. Infants lost to follow-up, whose parents refused consent, and babies who already progressed to higher stages of ROP requiring surgical management were excluded from the study, resulting in a total of 120 eyes of 60 infants.

Screening and detailed retinal examinations were carried out using an indirect ophthalmoscope equipped with a +28D or +20D lens. Pupils were widely dilated with phenylephrine 2.5% and tropicamide 0.5%, administered three times at 10-minute intervals, starting at 4 weeks or 28 days of life.

All neonates diagnosed with ROP and meeting the criteria for both laser treatment and anti-VEGF injection, as outlined by the ETROP[4,8] and BEATROP[7] trials, were randomly allocated into two equally distributed groups using a computer-based software (Random Allocated Software) via a simple randomization technique. This randomization was conducted irrespective of disease severity, gestational age, birth weight, birth order, mode of delivery, as well as maternal and neonatal risk factors. Group A comprised infants who received intravitreal Bevacizumab injections (0.625 mg intravitreally), while Group B consisted of infants treated with laser therapy using a frequency-doubled Nd: YAG laser.

Follow-up after treatment was conducted on Day 3, Day 7, at the 2nd week, the 3rd week, and then monthly until complete regression of the disease. The main outcome was considered after 1 year of follow-up as total regression of ROP or the treatment failure which is defined as the persistence or the recurrence of ROP. Postoperative observations at the time of follow up included signs of regression of the disease, the adverse events of the primary treatment, evaluation whether further treatment was necessary due to failure of primary treatment or any

progression of ROP.

Persistence of disease was documented if there was no regression of neovascularization and plus disease at 1 week of follow-up. ROP was considered recurrent if new extra retinal fibrovascular proliferation was observed, along with a halt in the anterior development of the vasculature during the follow-up period. Based on follow-up after primary treatment, eyes with persistent or recurrent disease were considered for retreatment either with an injection of Bevacizumab (0.625mg) or laser therapy aiming to achieve complete regression. Secondary outcome was recorded in retreated eyes as treatment failure or complete regression of ROP.

The collected data were statistically analyzed and compared using student independent T test and Chi-square test, with statistical significance set at $p < 0.05$ using IBM SPSS Statistics for Windows.

## RESULTS

During 1 year study period 338 babies who fulfilled inclusion criteria were screened for ROP. Out of 338 babies,157 babies developed ROP. The Incidence of ROP among the study population screened was 46.44%. Out of which,60 babies (120 eyes) with ROP which required treatment were randomly recruited in this study into group A and B, disease severity, gestational age, birth weight, birth order, mode of delivery, maternal and neonatal risk factors were statistically insignificant among the two groups. The baseline characteristics of the infants enrolled in the study has been described in table 1.

**Table 1: Characteristics Of The Infants Enrolled In The Study.**

| Characteristics | GROUP A (BEVACIZUMAB GROUP) | GROUP B (LASER GROUP) | p-value (95%C.I.) |
|---|---|---|---|
| Number of eyes | 60 | 60 | |
| Gender (Male/Female) | 17/13 | 15/15 | 0.604 |
| Gestational age-weeks | 29.8±1.75 | 30.5±1.8 | 0.132 |
| Birth weight (Grams) (mean±SD) | 1302.66±223.60 | 1286.37± 309.13 | 0.816 |

Abbreviation: C.I.: confidence interval, SD: standard deviation

Pre-plus disease was observed in 13(21.67%) eyes in group A and 18(30%) eyes in group B. Plus disease was observed in 37(61.67%) eyes and 34(54.67%) eyes in group A and group B respectively. Aggressive retinopathy of prematurity (AROP) was observed in 10 eyes (16.66%) in group A and 4 eyes (7%) in group B. Disease severity among the two groups is depicted in Table 2. Difference in disease severity among the two groups was statistically insignificant.

**Table 2: Showing Severity Of Disease Among Two Groups.**

| Stages of ROP | Group A | | Total | Group B | | Total |
|---|---|---|---|---|---|---|
| | Zones of ROP (n=60) | | | Zones of ROP (n=60) | | |
| | Zone 1 | Zone 2 | | Zone 1 | Zone 2 | |
| Stage 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Stage 2 | 5 (8.3%) | 35 (58.33%) | 40 (66.66%) | 1 (1.66%) | 41 (68.33%) | 42 (70%) |
| Stage 3 | 0 (0.00%) | 20 (33.33%) | 20 (33.33%) | 1 (1.66%) | 17 (28.33%) | 18 (30%) |
| Total | 5 (8.3%) | 55 (91.66%) | 60 (100%) | 2 (3.33%) | 58 (96.66%) | 60 (100%) |

Abbreviation: ROP: Retinopathy of prematurity

The need for retreatment was higher in Group A, compared to Group B. The higher requirement for re-laser in Group A was statistically significant, with a p-value of <0.05. Retreatment was performed on average 2.5 ± 0.97 weeks after the initial treatment for Group A and 2.3 ± 0.44 weeks for Group B, with the difference between the two groups being statistically insignificant. Details of the retreatments in both groups are provided in Table 3.

**Table 3: Comparison Of Retreatment Among Two Groups.**

| Add on Treatment | Group A(n=60) | | Group B(n=60) | | P-Value |
|---|---|---|---|---|---|
| | No. Of eyes | %age | No. Of eyes | %age | |
| Re-Laser | 26 | 43.33% | 9 | 15% | 0.02 |
| Re-Injection Bevacizumab | 6 | 10% | 2 | 3.33% | 0.38294 |
| Total | 32 | 53.33% | 11 | 18.33% | |

Among 120 eyes treated, 107 eyes showed total regression at different time durations, 49 eyes achieved regression in group A and 58 eyes achieved regression in group B. Total duration of regression was found to be statistically significant within 1 to 3 months of treatment with maximum regression of disease in group B. Duration of total disease regression in months among the two groups has been depicted in table 4.

**Table 4: Comparison Of Duration Of Total Disease Regression Among Two Groups**

| Duration of Total Disease Regression (months) | Group A (n=60) | | Group B (n=60) | | Total | 'p' Value |
|---|---|---|---|---|---|---|
| | No of eyes | %age | No. of eyes | %age | | |
| ≤1 Month | 11 | 18% | 17 | 28% | 28 | 0.292 |
| 1 to 3 months | 12 | 20% | 31 | 52% | 43 | 0.045 |
| 3 to 6 months | 13 | 22% | 5 | 8% | 15 | 0.354 |
| 6 to 12 months | 13 | 22% | 5 | 8% | 15 | 0.353 |
| Total | 49 | 82% | 58 | 97% | 107 | |

Among the 120 eyes treated, total regression was achieved in 49 eyes in Group A and in 58 eyes in Group B. In contrast, 11 eyes in Group A and 2 eyes in Group B failed to regress. The difference in total regression of ROP between the two groups was statistically significant, with a p-value of <0.05. A comparison of the final treatment outcomes between the two groups is presented in Table 5.

**Table 5: Comparison Of Treatment Outcomes Among Two Groups**

| Final Outcome | Group A | Group B | Total | 'p' value |
|---|---|---|---|---|
| Failure of Regression | 11 (18.33%) | 2 (43.33%) | 13 (10.83%) | 0.301 |
| Total Regression | 49 (81.67%) | 58 (96.67%) | 107 (89.17%) | 0.005 |
| Total | 60 (100.00%) | 60 (100.00%) | 120 (100.00%) | |

p=0.0082 (p<0.05; Significant)

Among the eyes treated in Group A, adverse events included vitreous hemorrhage in 3 eyes, development of cataract in 1 eye, progression to higher stages of the disease in 2 eyes, and vitreous bands in 1 eye. In Group B, transient red eye was observed in 1 eye, vitreous hemorrhage in 2 eyes, retinal hemorrhages in 3 eyes, and corneal haze in 2 eyes. The major limitation of our study is, small sample size and short follow up period of 12 months post treatment.

## DISCUSSION

In India, the incidence of ROP ranges from 38% to 47%.[9] In our study, 338 babies who fulfilled inclusion criteria were screened for ROP, out of which 157 babies developed ROP. The Incidence of ROP among the study population was 46.44%.

The mean gestational age was 29.8±1.75 weeks in group A and 30.5±1.80 weeks in group B. Zhang G et al[10] conducted a study in which their mean Gestational age was 28.96 ± 1.59 in Bevacizumab group and 28.27 ± 1.84 in laser group.

In the present study, the mean birth weight was 1302.66±223.60 grams in group A and 1286.37±309.13 in group B, there was no significance among the two groups with respect to birth weight. Karkhaneh R et al[10] conducted a randomized trial on 79 infants (158 eyes) in which mean birth weight was 1133±344 grams in injection bevacizumab group and 1202 ± 321 grams in laser group.

In the present study, among 60 eyes treated in Group A, it was found that stage 2 and stage 3 disease was 40/20 eyes in group A and 42/18 in group B respectively. A 2-year prospective randomized study done by Roohipoor et al[11] on 232 eyes from 116 preterm infants with Type 1 ROP reported stage 2 and stage 3 disease in 12/142 eyes in bevacizumab group and 6/72 in laser group respectively (p=0.56).

In the current study, there was a statistically significant difference between the groups A and B regarding the need for retreatment. In group A, failure of complete regression of disease requiring retreatment was more prevalent. 32 of the 60 eyes required retreatment in group A and 11 of the 60 eyes in group B required retreatment, this difference among the two groups was statistically significant. (p=0.02). In a randomized clinical trial, Karkhaneh et al[10] also found statistically significant-difference between the injection Bevacizumab and laser group regarding the need for retreatment; 9 out of 86 eyes in

the bevacizumab group and one out of 72 in the laser group required retreatment (p value= 0. 018).

In the group A, retreatment was done at a duration of 2.5±0.97 weeks after the initial treatment while in the group B, it was at 2.3±0.44 weeks. According to a randomized clinical trial done by Karkhaneh et al[10], in the Bevacizumab group, retreatment was performed at a mean of 5.07 ± 1.66 weeks after the initial treatment while in the laser group, it was at a mean of 3 weeks.

Our study showed that laser treatment was more effective compared to anti-VEGF in treating preterm babies with ROP with significantly reduced retreatment incidences. The statistical comparison of the time between the treatment and the retreatment did not reveal any significant difference. A meta-analysis conducted by Zhang et al in 2017[12] which included ten studies also found that laser treatment was more efficacious than anti-VEGF treatment with significantly reduced retreatment incidence in laser group.

In our study the primary outcome was recorded as regression of ROP or treatment failure that was persistence or recurrence of disease. Secondary outcome was recorded in retreated eyes as regression or failure of treatment. In our study among 120 eyes treated, 49 eyes (72%) achieved total regression of disease in group A and 58 eyes (97%) in group B after 12 months follow up period, this difference was statistically significant among two groups (p value=0.00545). It was observed that maximum disease regression was seen within 1 to 3 months post treatment follow up and it was 52 % in group A and 20% in group B, this difference was statistically significant among two groups

(p value=0.045). A randomized prospective study done by Roohipoor et al[11] to compare intravitreal Becvacizumab and laser photo-coagulation for type1 zone 2 ROP on 232 eyes from 116 preterm infants reported that out of 154 eyes in bevacizumab group 149 eyes (96.8%) showed the complete or near complete regression of ROP with regression of IVB injection was observed in all the patients. In Laser group regression of ROP in 76/78 eyes (97. 4%). No patients required retreatment. The difference in results in our study and Roohipoor et al[11] study may due to patient enrolment and follow up period. In Roohipoor et al[11] study only infants with type 1 zone 2 were enrolled and followed up the infants after treatment until 90 weeks postmenstrual age.

In our study, the adverse events observed in group A were vitreous hemorrhage in three eyes, cataract development in one eye, 2 eyes of preterm babies progressed to higher stages of disease, either stage 4a, 4b or 5 and were referred to higher center, vitreous bands were seen in 1 eye. The adverse events associated with group B were transient corneal haze in 2 eyes, transient red eye in 1 eye, vitreous hemorrhage in 2 eyes, retinal hemorrhages in 3 eyes. There were no cases of endophthalmitis, intraocular inflammation and systemic side effects. A 5-year retrospective analysis by Hwang et al[13] to determine outcomes after treatment on 54 eyes with Type 1 ROP found that pre-retinal or vitreous hemorrhage occurred in 4/22 eyes (18%) treated with injection bevacizumab, no corneal or lenticular opacities were seen and no systemic effects related to injection bevacizumab were reported. In PRP treated eyes, pre-retinal or vitreous hemorrhage not involving visual axis or requiring vitrectomy occurred in 3/32 eyes (9%), only one eye went on to retinal detachment and 5 eyes developed macular ectopia in PRP treated group. Both IVB and PRP treated ROP eyes were associated with high refractive errors.

There were some limitations in our study. The most important of them is small sample size and short follow up period of 12 months post treatment.

## CONCLUSION

ROP remains a leading cause of vision problems worldwide, with increasing cases in developing countries. Both frequency-doubled Nd-YAG laser photocoagulation and intravitreal Bevacizumab injections are effective treatments for Type 1 ROP. However, laser treatment proves more effective, with fewer retreatments and treatment failures. Bevacizumab injections are beneficial in reducing the severity of AROP during initial treatment. Overall, laser therapy is more successful in achieving complete regression of ROP with fewer recurrences. Regular monitoring and close supervision are necessary until the retina is fully vascularized. Effective screening of all premature infants and timely interventions significantly improves visual and structural outcomes in ROP.

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