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# OUTCOME OF THE MANAGEMENT OF AGGRESSIVE RETINOPATHY OF PREMATURITY (A-ROP)

Ophthalmology

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## ABSTRACT

**Objective:** To compare the efficacy and safety between laser therapy and anti-vascular endothelial growth factor (VEGF) agents for aggressive retinopathy of prematurity (A-ROP). **Patients and methods:** A comparative study for laser, anti VEGF with laser and anti-VEGF mono therapy for A-ROP treatment. Study period was 2016 to 2020 at BIRDEM General Hospital. We included fifteen A-ROP babies with thirty eyes. Ten eyes treated with laser, ten eyes treated with anti-VEGF with laser and ten eyes treated with anti-VEGF. We used Bevacizumab as anti-VEGF. We compared efficacy, safety, complication, retreatment between these three groups. **Result:** Complication incidences were significantly higher in laser therapy group. 20% of infants' needs retreatments with laser therapy more than two sessions. In anti-VEGF and laser therapy group, 6.7% of infants need retreatment and in anti-VEGF group-1 3.3% infants need retreatment. P-value was 0.005 which is significant. Development of myopia is significantly higher in laser therapy group (Group-3). About 100% infants' developed myopia. In Group-2 30% infants' developed myopia. In Group-1 no infants developed myopia. P-value was highly significant 0.01. **Conclusion:** This analysis outcome indicates anti-VEGF agents are as effective as laser treatment and safer than laser. The degree of myopia in A-ROP in laser group is higher than anti-VEGF mono therapy group. The decreased incidence of early unfavorable refractive and functional outcomes in the IVB group compared with the laser group showed a potential benefit for patients treated with Intravitreal Bevacizumab (IVB).

## KEYWORDS

A-ROP, Laser, Anti-VEGF, Myopia, Outcome

## INTRODUCTION

Retinopathy of prematurity (ROP) is an important cause of childhood blindness worldwide, and the incidence is rising. It is caused by poor retinal vascular development. High Oxygen concentrations used or adjuvant oxygen therapy because of immature respiratory function have been the major risk factor for ROP. Other risks for ROP include gestational age (GA) and birth weight[1,2]

About 10% of diagnosed ROP cases in India is R-ROP. Aggressive retinopathy of prematurity (A-ROP) is the most severe form of ROP characterized by apparent disproportionate plus disease compared with peripheral disease findings in Zone I or posterior Zone II. The diagnosis of A-ROP is clinically important in ensuring timely intervention as A-ROP can rapidly progress to tractional retinal detachment which leads to blindness. Further higher rates of unfavorable structural and refractive outcomes have been reported following laser ablation and cryoablation for the treatment of A-ROP.[3-6]

In the recent years, several studies have reported promising results with anti-vascular endothelial growth factor (VEGF) inhibitors, particularly Bevacizumab, for the treatment of A-ROP. Lesser refractive errors have been demonstrated following Intravitreal Bevacizumab (IVB) therapy compared to laser treatment. However, there have been few studies assessing refractive and functional outcomes following IVB treatment for A-ROP. [7-10] We therefore aimed to determine the 2-year clinical outcomes between laser therapy and anti-vascular endothelial growth factor (VEGF) agents for aggressive retinopathy of prematurity (A-ROP).

## PATIENTS AND METHODS

Total fifteen infants diagnosed as A-ROP. Total thirty eyes were included in this study. This prospective Quasi study was conducted in the department of ophthalmology BIREDEM general hospital from January 2016 to December 2020.We divided these thirty eyes in three groups. All thirty patients were divided into groups. Group-1 ten eyes treated with anti-VEGF (Bevacizumab) as mono therapy. Group-2 included ten eyes treated with anti-VEGF and laser. Group-3 included ten eyes treated with laser. We observed the vascularization of the retina need of retreatment and the complications of the treatment. We keep follow up these infants accordingly up to two years. We recorded the refractive status of the treated eyes. Variables include gender, gestational week, body weight, treatment strategies, and patients' refractive errors, all are studied in this study. All the relevant data were recorded in a predesigned datasheet. Statistical analysis was carried out using SPSS (statistical package for social sciences) statistics V 26.0 Software. Data were compiled, checked edited properly before analysis. An appropriate test of significance (chi-square test) was used for the statistical analysis. The Ethical Consideration will be maintained according to declaration of Helsinki.

## RESULT

The Mean ± SD, and 95% of CI of gestation age were 29.13 ± 1.60 week, 28.41 to 29.86 week respectively. The gestational age range was 26 weeks to 32 weeks with the median was 29 weeks. Female infants were 46.7% and male infants was 52.7%. The Mean ± SD of birth weight was 1.4 ± 0.219 kilogram, with the range from 1000 gm to 1800 gm.

**Table 1: Sociodemographic and Anthropometric Parameters of the Study Subjects**

| | Group 1 | Group 2 | Group 3 | Total | P value |
|---|---|---|---|---|---|
| ***Body Weight*** | | | | | |
| 1.00 Kg | 0 | 2 (6.7%) | 0 | 2 (6.7%) | |
| 1.20 Kg | 4 (13.3%) | 2 (6.7%) | 0 | 6 (20%) | |
| 1.30 Kg | 2 (6.7%) | 2 (6.7%) | 2 (6.7%) | 6 (20%) | |
| 1.40 Kg | 0 | 2 (6.7%) | 4 (13.3%) | 4 (13.3%) | 0.014* |
| 1.50 Kg | 2 (6.7%) | 0 | 0 | 4 (13.3%) | |
| 1.60 Kg | 0 | 0 | 2 (6.7%) | 2 (6.7%) | |
| 1.70 Kg | 2 (6.7%) | 2 (6.7%) | 0 | 4 (13.3%) | |
| 1.80 Kg | 0 | 0 | 2 (6.7%) | 2 (6.7%) | |
| Total | 10 (33.3%) | 10 (33.3%) | 10 (33.3%) | 30 (100%) | |

Chi-square test has been performed.

There was no significant relation among the gender regarding A-ROP treatment but in case of low birth weight and early gestational age is a major risk factor for regressing avascular area and plus diseases of A-ROP treatment and desire several times retreatment and frequent follow up.

**Table 2: Distribution of Multiple session of Laser Photocoa gulation**

| Retreatment | Group 1 | Group 2 | Group 3 | Total | P Value |
|---|---|---|---|---|---|
| Need 2nd dose | 1 (3.3%) | 0 | 0 | 1 (3.3%) | |
| Need 2nd dose, Anti VEGF | 1 (3.3%) | 0 | 0 | 1 (3.3%) | |
| Need another 2-session laser | 0 | 2 (6.7%) | 6 (20%) | 8 (26.7%) | |
| Need another single session laser | 0 | 1 (3.3%) | 0 | 1 (3.3%) | 0.010* |
| Need few laser | 1 (3.3%) | 0 | 0 | 1 (3.3%) | |
| No Need | 7 (23.3%) | 7 (23.3%) | 4 (13.3%) | 18 (60.0%) | |
| Total | 10 (33.3%) | 10 (33.3%) | 10 (33.3%) | 30 (100.0%) | |

Both three groups regression of avascular area and plus diseases observed within seventy-nine weeks but in Group-1 we advised another dose of anti-VEGF for two eyes as the vascularization of retina was very slow and in case of one infant, we switched to laser treatment as the infant was not in situation of frequent follow up. In Group-2 two eyes need two session laser treatment and one eyes need another session laser treatment accordingly. In Group-3 six eyes need more than two session laser treatment. Group-1 has minimum retreatment condition.

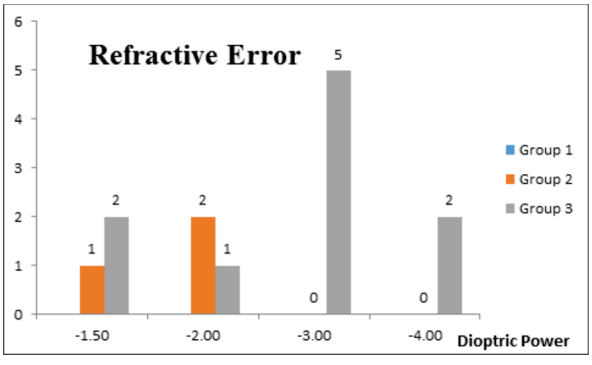
**Table 3: Distribution of several times of Laser treatment**

| Laser | Group 1 | Group 2 | Group 3 | Total | P Value |
|---|---|---|---|---|---|
| Need 2 times laser | 1 (3.3%) | 0 | 0 | 1 (3.3%) | 0.005* |
| Need 3 times laser | 1 (3.3%) | 0 | 0 | 1 (3.3%) | |
| Need laser several time | | 2 (6.7%) | 6 (20%) | 8 (26.7%) | |
| Need laser single time | 0 | 1 (3.3%) | 0 | 1 (3.3%) | |
| Need more than 3 times laser | 1 (3.3%) | 0 | 0 | 1 (3.3%) | |
| No Need | 7 (23.3%) | 7 (23.3%) | 4 (13.3%) | 18(60%) | |
| Total | 10 (33.3%) | 10 (33.3%) | 10 (33.3%) | 30 (100.0%) | |

In this table shows that Group-3, six infants need more than two times laser treatment of two years, and the p value was significant in case of several times laser issues. So, with anti-VEGF as mono therapy we can avoid several times laser which is painful and hazard to the infants.

No complications related to IVB (Intravitreal Bevacizumab) were observed including iatrogenic cataract, endophthalmitis, retinal detachment, and vitreous hemorrhage.

Retinal examination at an adjusted age of two years demonstrated successful retinal vascularization in Group-1, Group-2, and Goup-3. According to refractive analysis at an adjusted age of two years more degree of myopia showed in Group-3.




**Graph-1: Distribution of Refractive Error (Myopia) after 1 year 6 months**

## DISCUSSION

Aggressive retinopathy of prematurity (A-ROP) is the recent term, previously known as aggressive posterior retinopathy of prematurity (APROP), occurs usually in extremely premature infants less than 28 weeks of gestational age with very low birth weight of ≤1 kilogram. Retinopathy of prematurity (ROP) screening is essential for the presence of risk factors such aspremature birth, low birth weight, received supplemental oxygen, intraventricular hemorrhage, and history of maternal chorioamnionitis.[11,12] The management of A-ROP requires frequent screening examinations and timely intervention as mentioned in the Early Treatment Retinopathy of Prematurity Study.[13] Laser therapy is the gold standard for the treatment of ROP.[2,9,10,12-14]The progression of the disease is found in 12% of eyes despite the treatment. The recent modalities of the treatment of ROP, are anti-VEGF, beta-blockers, or insulin-like growth factor gene therapy.[14]

In this study, the mean gestational weeks was 29.13 with the range from 26 weeks to 32 weeks. The was no significant difference between Female and male infants. The Mean ± SD of birth weight was 1.4 ± 0.219 kilogram, with the range from 1.0 kilogram to 1.8 kilogram.

The reported Mean (±SD) birth weight is 1,259.66 (±310.51) gm with the range from 660 gm to 2,000 gm. The mean (±SD) gestational age is 29.75 (±2.35 weeks) with the range from 26 weeks to 36 weeks. The birth weight is more than 1250 gm in 48% of the infants.[12] Other study showed the Mean gestational age is 29.1 weeks, and the mean birth weight is1226.9 gm. [15]

Intravitreal Bevacizumab (IVB) has been utilized as mono therapy and as a supplement to laser ablation for A-ROP and provides successful and prompt disease regression without serious complications. We demonstrated regression with successful anatomical outcomes in all infants who received IVB as a single treatment modality for A-ROP. It has also been suggested that aggressive cases may require additional IVB injection due to prevent diseases recurrence. Two infants required additional IVB treatment due to diseases recurrence with vascular engorgement and neovascular proliferation at approximately 40 weeks. Re-injection of IVB was performed in these cases with peripheral retinal vascularization achieved without any complications observed at follow-up of 79 weeks.

On the other hand, laser treatment is a highly destructive procedure in A-ROP in which most of the retinal tissue is ablated preventing the growth of vessels peripherally from the point of treatment. Furthermore, risk of retinal detachment has been reported even after successful laser treatment in such case.

Several studies reported on laser therapy as the primary treatment modality of aggressive retinopathy of prematurity. [13,16] All patients were undergoing peripheral laser ablation for their eyes. Success is estimated as complete regression of the disease without require for any other treatment modality. About one-third of eyes required a second session of laser. About 15% to 30% of eyes reported unfavourable outcomes of A-ROP that was progressed to retinal detachment compared to other treatment modalities.[2,7,13,16-18] Retinal detachment was successfully managed by lens-sparing vitrectomy. [13] About 71% to 97% reported a good anatomic outcome. [12.16]

A combination therapy of intravitreal injection of anti-VEGF and laser photocoagulation is an effective and safe modality of treatment for Type I ROP and A-ROP. [15,19] 82 eyes were treated with anti-VEGF and laser photocoagulation, 95% eyes had attached retina at 52 weeks follow up. [15]

In our study, the combination treatment modalities including ant-VEGF injection and laser therapy was effective, no complications were noted during the follow up time. Myopia progression is observed in 30% infants of group 2.

A Turkey study reported no retinal detachment was observed in the 25 cases of intravitreal injection of Bevacizumab group but 2 out of 11 cases of A-ROP treated with laser therapy 0/25 and 2/11 eyes progressing to retinal detachment. [9] Other study by Nicoara et al reported the success rate of 94% in anti-VEGF group compared to 83% in laser therapy group. [20] Intravitreal ant-VEGF (Bevacizumab), often with adjuvant laser photocoagulation, lead to regression of the disease without retinal detachment in all (100%) eyes, and most children retain functional vision. [19] Recently, many studies have reported late reactivation of disease with anti-VEGF. The long term follow up is required. [21-24]

Laser photocoagulation for ROP is associated with restricted visual field [25,26] and refractive error. [27,28] It is thought that the increased number of laser ablation spots might induce myopia. [29] Prevalence of high myopia reported in literature varies from 8% to 35% of babies who were received laser therapy. [27,30,31] Myopia and restricted visual field are the main adverse events associated with laser therapy rather than other treatment modalities. [25-28]

These studies demonstrated laser photo-coagulation results in better anatomic results and causes lower degrees of myopia than cryoablation. However, laser treatment for A-ROP has been shown to be associated with a range of unfavorable anatomic and functional outcomes depending on disease severity. The introduction of IVB to ROP therapy has allowed most cases of A-ROP to be salvaged with successful anatomic outcomes. In recent years, a few studies have been assessed refractive outcomes following IVB treatment and

demonstrated IVB in ROP is associated with a lower rate of refractive disorder compared to laser ablation.

## CONCLUSION

This study indicates anti-VEGF are as effective as laser treatment, safer and less hazardous than laser treatment. Most important is anti-VEGF as mono therapy for APROP can prevent development of myopia of premature infants after regression of APROP, which is a complication of aggressive laser therapy needed for APROP treatment.

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