

## EVALUATING EFFECTIVENESS OF LASER PHOTOCOAGULATION AND INTRAVITREAL ANTI-VEGF INJECTIONS IN STAGE III RETINOPATHY OF PREMATURITY

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### ABSTRACT

**Purpose:** To compare the effectiveness of anti VEGF and laser photocoagulation treatment in stage III retinopathy of prematurity in infants at tertiary care hospital in central Gujarat.

**Methods:** This was a comparative prospective and retrospective observational study. 60 infants were diagnosed with stage III retinopathy of prematurity from which 20 infants were treated with laser and 40 infants treated with anti VEGF injection of 0.25 mg/0.025 mL Ranibizumab. Efficacy of both the treatments were compared in terms of regression of disease clinically. All Demographic and medical data was analyzed using MS excel for finding frequency, percentages and associations applying Chi-squared test and by Epi info™ (version-7.2.5).

**Result:** In this study 32(80%) infants who received anti VEGF and 8(40%) infants who received laser treatment showed stopped progression of neovascularization in single dose. Only 8(20%) infants needed re-treatment anti VEGF injection while 11(55%) infants required re-treatment laser therapy. So there was a statistically significant higher recurrence rate among infants who underwent laser therapy as compared to infants who underwent anti VEGF therapy ( $P=0.006$ ). 1(5%) infant lost both his eyes even after being treated with 2 sittings of laser treatment and who was <800g and very pre term birth so even with effort to treat, there was no regression and infant developed retinal detachment in both eyes.

**Conclusion:** Both the treatments are effective for treating ROP stage III infants but higher recurrence rate was found among infants who underwent laser therapy as compared to anti VEGF therapy.

**Keywords:** Anti vascular endothelial growth factor, laser treatment, Retrolental fibroplasia

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**INTRODUCTION**

Retinopathy of prematurity (ROP) is a retinal Vaso- proliferative disease that affects premature infants. ROP is a leading cause of childhood blindness worldwide. [1]The World Health Organization's "Vision 2020 program" has identified ROP as an important cause of blindness in both high- and middle-income countries. [2,3]

Development of ROP and effectiveness of treatment at an appropriate stage makes it amenable for systematic screening. It is a disorderly and abnormal development of retinal blood vessels in premature babies. Treatment of ROP is based on the principle of retinal ablation. Treatment is directed to the avascular part of the retina with the goal of decreasing the production of angiogenic factors. In 1988, cryotherapy was recommended for stage III+ ROP. In the 1990s, treatment of stage 3+ disease underwent a slow transition from cryotherapy to laser therapy. Both these treatments destroy the majority of the cells that produce vascular endothelial growth factor (VEGF) in the retina. Conventional laser therapy for zone I retinopathy of prematurity is successful in approximately 50% of cases but inevitably causes permanent loss of the peripheral visual field and often induces clinically significant myopia. Hence, the use of anti VEGF agents is an emerging treatment for ROP now a days. [4]

The purpose of the study to compare the effectiveness of treatment, anti VEGF and laser photocoagulation in stage III ROP at a medical college-associated tertiary care hospital in central part of Gujarat.

**METHODS**

After getting permission from the institutional ethics and research committee, the study data was

collected in retrospective and prospective manner. Retrospectively data was collected from available records. Examination details of infants who were screened and diagnosed with stage III ROP and treated by any of the method of treatment i.e. anti VEGF or laser were included in the study. For prospective study, ophthalmological examination of ROP was performed by doing funduscopy. First examination was performed between 4 and 6 weeks of chronological age. Each patient was classified according to International Classification of Retinopathy of Prematurity. [5] We selected treatment needs for stage III ROP infants as established by the Early Treatment for Retinopathy of Prematurity (ETROP) protocol.[6] After a written informed consent from the parents, an initial intravitreal injection of 0.25 mg/0.025 mL Ranibizumab or laser photocoagulation was given to diseased eye. The outcome included- complete or incomplete peripheral vascularization, ROP recurrences requiring re treatment for both treatment modalities. The final clinical status of the retina was evaluated for each patient. The outcome was labelled by the vitreoretinal surgeon as the retinal status of vascularization which showed improvement (peripheral vascularization) after treatment or no improvement and according to that further follow ups were decided by the specialist. Infants treated with anti VEGF and laser photocoagulation were examined a week after treatment to monitor for signs of any complications, then followed up as per clinical requirement and effectiveness of treatment, weekly or biweekly until the first 3 months or till regression of ROP (full normal development of vasculature)

whichever was earlier. All the treatments and follow ups were done by the same surgeon. All Demographic and medical data was analysed using MS excel for finding frequency, percentages and associations applying Chi squared test and by Epi info <sup>TM</sup>. (version-7.2.5)

#### Inclusion Criteria:

1. Stage III ROP infants who had received the anti VEGF (Ranibizumab) injection
2. Stage III ROP infants who had received laser treatment
3. The patients who were regular on follow up for at least 3 months from the day of initiation of treatment.

#### Exclusion Criteria:

1. Infants of stage III ROP who did not come for treatment or who were not getting treatment.
2. Infants who didn't come for follow up.
3. Infants who expired within 3 months of their follow up period from the initiation of their treatment.
4. Infants who were given combination treatment of anti VEGF and laser therapy.

#### Study Design:

Observational prospective and retrospective study

#### RESULTS

The study was conducted among total 1432 infants for a period 1 year from June 2020 to June 2021. Total of 1432 infants screened, among them 123 infants were diagnosed with ROP of different stages. Among these 93 infants required treatment, either anti VEGF injection or laser treatment. Total 60 infants out of 93 were diagnosed with stage III of ROP and given treatment and were included in this study. Out of all the study participants, 20 infants were included in laser treatment group (Laser group) while 40 were included in intravitreal anti VEGF injections group (Anti VEGF group) by systemic

random sampling method. Study participants were chosen in the ratio of 1:2 because resources of the laser photocoagulation is less than half as compare to anti VEGF in given study area.

In our study, we observed the distribution of the eye involvement among infants of both groups. Bilaterality was found in majority, in 50 (83.3%) infants out of 60. Among the laser therapy group, right eye was involved in 4 (20%) infants and left eye involved in 2 (10%) infants while both eyes were involved in 14 (70%) and 36 (90%) infants in laser therapy group and anti VEGF group respectively. The sex distribution of the infants in our study showed that, of the total infants involved in laser therapy group, 9 (45%) were male while 11 (55%) were female. Among anti VEGF therapy group, 23 (57.5%) were male while 17 (42.5%) were female.

We distributed infants according to their age into 3 groups viz- 31-34 weeks, 35-38 weeks and 39-42 weeks. We found that majority of infants 53.3% (32 infants out of 60) who were treated with either laser or anti VEGF were between 31-34

Table 1. Distribution of the infants' weight among both the groups

Weight of infants (g)	Treatment group				Total
	Laser group		Anti VEGF group		
	N*	% <sup>+</sup>	N*	% <sup>+</sup>	
500-1000	6	30.0%	4	10.0%	10 (16.7%)
1001-1500	11	55.0%	26	65.0%	37 (61.7%)
1501-2000	2	10.0%	10	25.0%	12 (20.0%)
2001-2500	0	0%	0	0%	0 (0.0%)
2501-3000	1	5.0%	0	0%	1 (1.7%)
Total	20	100%	40	100%	60 (100%)

weeks of age and very few only 8.3% (5 out of 60) were between 39-42 weeks of age. [Figure-a]

35.5 ( $\pm 2.3$ ) weeks and for anti VEGF group mean PMA was 34.4 ( $\pm 2.3$ ) weeks. [P value: 0.092 (t-test calculated using Epi info™)]

**Table 2. Rate of the recurrence among both the groups after dose of treatment**

Treatment group	Effectiveness in single dose		Recurrence (Need for re-treatment)		No effect	
	N*	%+	N*	%+	N*	%+
Laser group (N=20)	8	40%	11	55%	1	5%
Anti VEGF group (N=40)	32	80%	8	20%	-	-
Overall	40	66.7%	19	31.7%	1	1.7%
P value	0.002		0.006		NA	

\*- Frequency

+ - Percentage

Majority of infants who were treated with any of the modality laser or anti VEGF injection were having weight between 1001–1500 g which is in category of very low birth weight (VLBW) [Table-1].

**Table 3. Profile of average time taken for good regression among both groups**

Treatment group	Average time of good regression (in weeks)			P value
	Mean	S.D.	Range	
Laser group (N=20)	9.6	3.2	6-15	0.127
Anti VEGF group (N=40)	11.1	3.7	5-26	
Overall	10.4	3.5	5-26	-

As per screening criteria infants of <1750 g of birth weight or >1750 g of birth weight but having high risk factors were screened, and in our study only 1 (1.7%) such infant was having weight >1750g and he was managed with laser treatment. As ROP is disease of prematurity so we also included, average post-menstrual age (PMA) at presentation among both the groups at the time of first examination. Mean PMA for laser group was

disease after first dose. We compared the effectiveness of both treatments in terms of regression after 1<sup>st</sup> dose which showed that 32 (80%) infants in the anti VEGF group and 8 (40%) infants in the laser treatment group had stopped progression of neovascularization. Only 8 (20%) infants in the anti VEGF injection group required re treatment as against 11 (55%) infants in the laser therapy group. [Table 2]

We further evaluated the therapy in terms of time taken for regression of disease in weeks and comparison of both groups is shown [Figure-b].

Out of all patients who were treated with the laser therapy, 17 (85%) patients reported good regression within 5 to 12 weeks and remaining 2 (10%) patients within 13 to 19 weeks while 1 (1.7%) patient reported no effect at final follow-up who lost his eyes.

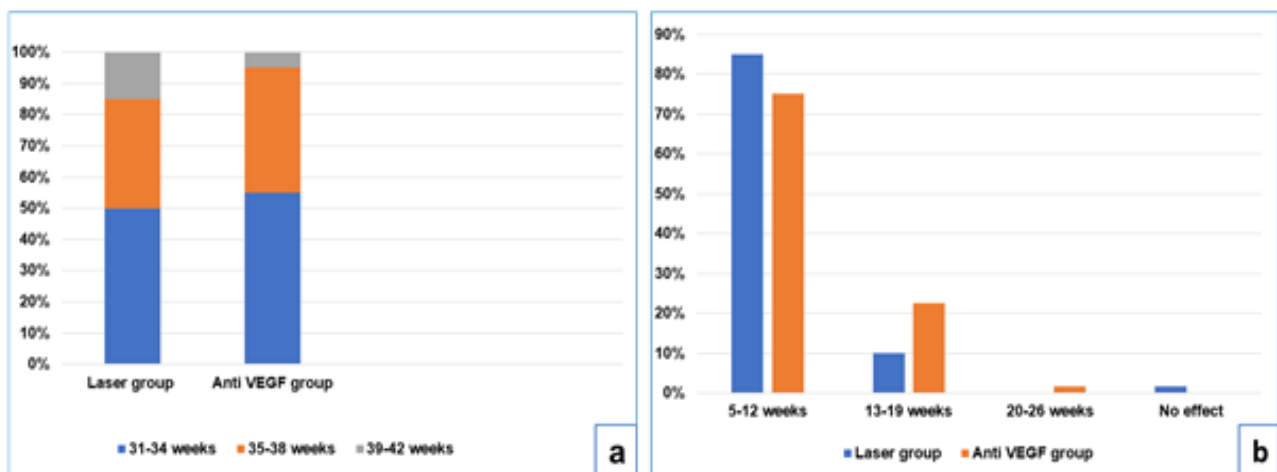


Figure 1: a) Age distribution of the infants among both groups b) Average time taken for good regression after treatment

Out of all patients who were treated with anti VEGF, 30 (75%) patients showed good regression between 5 to 12 weeks while remaining 10 (24.2%) patients showed good regression between 13 to 26 weeks. Mean time taken for good regression was higher among infants who underwent anti VEGF therapy (11.1 weeks) as compared to the infants who underwent laser therapy (9.6 weeks) [Table-3]. As a part of follow up after treatment, we also observed the complications- among anti VEGF group sub-conjunctival haemorrhage was observed among 4 (10%) infants while among infants from the laser therapy group, cataract was observed in 1 (5%) infant as the complication.

## DISCUSSION

This was a prospective and retrospective cohort study. Total 1432 infants during one year period were screened. Among them 123 infants were diagnosed with different ROP stage. Total 60 infants fitting into the inclusion criteria were included in our study. Out of all the study participants, 20 infants were included in laser treatment group (Laser group) while 40 were included in intravitreal anti VEGF injections group (Anti VEGF group).

In present study, bilateral eye involvement was found to be higher proportion in both groups, 90% and 70% in anti VEGF group and laser therapy

group respectively. In study conducted by Hwang et al [7], a total of 54 eyes (96.4%) from 28 patients were included and their study too showed a higher bilateral eye involvement among patients. Sex distribution in present study, among the infants enrolled in laser therapy group, 9 (45%) were male and 11 (55%) were females, while in anti VEGF therapy group, 23 (57.5%) were males and 17 (42.5%) were females. The sex distribution ratio of infants involved in laser therapy group was nearly one while in case of anti VEGF group the proportion of males was almost double than the females. Similar sex distribution was also observed by the study done by Isaac M et al. [8] during the year 2009 to 2013 in one of the hospitals of Toronto, while study done by Gunay M et al.[9] in Turkish city observed similar proportion of males and females in both the comparison groups. Majority of infants who were given anti VEGF injection and laser treatment were between age group of 31 to 34 weeks of age in our study. There were very few infants in age group of 39 to 42 weeks who were given treatment. Chandra et al [10] in their review article, reported that the median age at detection of stage 1 ROP was 34 weeks. If it progresses in severity, ROP needing treatment appears at 34 to 38 weeks.

These findings were comparable with our study. As per screening criteria infants of <1750 g of birth weight or >1750 g of birth weight but having high risk factors were screened, and only 1(1.7%) infant was treated with laser treatment in our study. In the laser group, half of infants had birth weight in the range of 1001-1500 g. In anti VEGF also more than half of the infants were from this birth weight group in our study. Since ROP is a disease of prematurity, low birth weight is one of the major risk factors for disease progression and regression, study done by Isaac M et.al [8] recorded different birth weight group (500–1000 g) in more proportion. They reported 722g as median in anti VEGF while 640g as median in laser group. Gunay M et.al [9] also observed that most of the infants were having birth weight in the range 500–1000g. The average post-menstrual age was found to be 35.5 weeks and 34.4 weeks in laser therapy group and anti VEGF therapy group respectively while the overall mean post-menstrual age was 34.8 weeks in present study. A study done in Turkish city found mean post menstrual age as 35 weeks in anti VEGF group while 36.03 weeks for the laser group. This was a retrospective study evaluating IVB, IVR, and LPC in the treatment of ROP. The data was obtained from the two referral centers for ROP treatment in two Turkish cities by Gunay M et.al. [9]

We observed that 20% of infants treated with anti VEGF and 55% treated with laser therapy had recurrence. This was different from the study done by Wang SD et.al [11] among Chinese infants. In their study a total of 26 eyes of 13 infants (52%) developed ROP recurrence after a single-dose injection in the IVR group. Meanwhile, 2 eyes of 1 infant (4%) developed ROP recurrence after laser photocoagulation in the laser therapy group. Agreeing with our study intravitreal injection of bevacizumab monotherapy (6%) as compared with laser (26%) showed significant lower recurrence rate for Zone I Stage 3+ ROP in BEAT-ROP study. [12] A total of 22 (13.7%) laser-treated and 15 (9.8%)

ranibizumab treated eyes had recurrences that required further intervention in the study done by Kang H et.al [13] The mean for interval of retreatment was 2.3 weeks for the laser group and 5.7 weeks for the Ranibizumab group. In the study done by O'keeffe N et.al [14] four of 14 eyes (28.6%) had recurrence of ROP; three eyes (21.42%) which had bevacizumab treatment and one eye (7.14%) with conventional laser therapy. The Meta-analysis done by Wang et.al [11] which included 2835 eyes totally comparing the efficacy of anti VEGF intravitreal injections monotherapy and laser therapy for ROP showed no overall difference on recurrence outcome and retreatment outcome, which implied that both anti VEGF monotherapy and laser therapy for ROP had similar therapeutic efficacy. Several reports indicated late recurrence of ROP after different anti VEGF treatment. [15-17] In our study 32(80%) infants were having good effect with single dose of intravitreal injection of anti VEGF while only 8(20%) infants were having good effect of laser treatment. Only 8(20%) infants needed re-treatment with anti VEGF injection while 11(55%) infants required re-treatment in laser therapy group. P value was 0.006 which was also statistically significant showing the significantly higher recurrence rate among infants who underwent laser therapy as compared to infants who underwent anti VEGF therapy. We found that the average time taken for good regression was higher among infants who underwent anti VEGF therapy (11.1 weeks) as compared to the infants who underwent laser therapy (9.6 weeks). However, this difference was statistically not-significant. P value for this was 0.127. Aldebasi T. et.al [18] in Saudi Arabia observed in their study that all 37 patients had regression of ROP within 10 weeks of injection, 21 patients (56.8%) had regression of ROP within 7 weeks of injection.

Gestational age, birth weight, gender, or conceptual age at the time of injection were also not related to earlier regression of ROP (within 7 weeks) Chen et.al [19] compared the efficacy of intravitreal Ranibizumab with bevacizumab in two groups of premature children with ROP. The authors concluded similar efficacy of both drugs in terms of regression of the disease. Another retrospective study conducted by Aldebasi T. et.al. [18] in Brazil compared the results obtained with intravitreal Ranibizumab treatment alone and combined treatment with Ranibizumab and laser photocoagulation. 87.5% of the cases showed favorable results in terms of regression of neovascularization with Ranibizumab (0.25 mg) in 16 eyes, while 12.5% of the patients had unfavorable results in the form of disease progression to stage 4 and 5. In the group treated with Ranibizumab and laser, favorable results were only achieved in 70.7% of the eyes.

In our study, the rate of post-operative complication was higher among patients of anti VEGF group (10%) as compared to laser therapy (5%). The complication like sub-conjunctival haemorrhage was observed in antiVEGF group patients and cataract was observed in laser therapy group. Findings of our study are comparable with the study conducted by Aldebasi et al [18] They had conducted study to evaluate the efficacy of anti VEGF for the treatment of retinopathy of prematurity (ROP). In their study they reported subconjunctival haemorrhage in 10.8% patients. In contrast to the present study, a metaanalysis done by S.D.Wang et.al [11] showed that complication of anti VEGF intravitreal injections monotherapy and laser therapy showed a significant difference favoring the laser group (OR: 0.38, 95%CI: 0.19–0.75,  $P=0.005$ ) having higher complications incidence with moderate heterogeneity between studies.

## CONCLUSION

Our study concluded that both the treatments are effective for treating ROP stage III infants but higher recurrence rate was found among infants who underwent laser therapy as compared to the ones who underwent anti VEGF therapy. Although effectiveness in infants who underwent laser therapy was observed within a shorter time duration (9.6 weeks) than the effectiveness observed after giving anti VEGF therapy (11.1 weeks). But, giving intravitreal anti VEGF is more convenient in infants than giving laser therapy. Early treatment is found to be more effective, independent of the modality of treatment (anti VEGF or laser therapy). Thus, either of the treatments can be given according to the setup and availability as long as it is given early during the course of disease for better results. Earlier the treatment given during the course of disease, better is the regression and requirement of retreatment is also reduced. Therefore, the need for early diagnosis cannot be overemphasized which is possible only by regular screening of infants in ROP clinics.

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