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Follow-Up Compliance in Retinopathy of Prematurity Care: A Bangladeshi Perspective

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ABSTRACT

Background: Retinopathy of Prematurity (ROP) is a vaso-proliferative disorder that can lead to irreversible vision loss without timely treatment. Moreover, regular follow-up after treatment is crucial for successful outcomes. However, follow-up compliance in Bangladesh remains suboptimal. This study aimed to assess adherence to treatment and follow-up in ROP care. ***Methods:*** A retrospective study was conducted at Bangabandhu Sheikh Mujib Medical University to assess compliance with treatment and follow-up among infants with Retinopathy of Prematurity (ROP) who received intravitreal anti-VEGF injection (Avastin), laser photocoagulation, or a combination of both between January 2021 and December 2023. ***Result:*** A total of 950 preterm babies were screened. Intravitreal Avastin was required in 127 (13.4%), laser therapy in 118 (12.4%), and both treatments in 43 (4.5%). Surgical intervention was needed in 27 (2.8%) babies. Type 1 ROP occurred in 295 (31.1%), aggressive ROP in 130, stage 3 (zone II/III) in 50, stage 4 (A+B) in 19, and stage 5 in 14 babies. Mean gestational age was 33.4 ± 2.8 weeks and mean birth weight 1795 ± 300 g. Compliance with intravitreal injection was 100% initially, declining to 31.4% by 16 weeks, while laser follow-up ranged from 97.6% at week 1 to 61.6% at week 12. Rescue laser was required in 43 babies initially treated with intravitreal injection. ***Conclusion:*** Compliance with ROP treatment follow-up was satisfactory in both groups during the first month but declined thereafter. Follow-up was not maintained for all infants up to six months of age, which is the protocol recommended by most ROP specialists.

Keywords: *Retinopathy of prematurity, Treatment, Post-treatment follow-up, Compliance*

1. INTRODUCTION

Retinopathy of prematurity (ROP) is a potential blinding condition that affects premature infants, and requires timely intervention. It is one of the major ocular disease, which can contribute to nearly 40% of childhood blindness in resource-poor countries.[1] Advancements in neonatal medical care have significantly increased preterm infant survival rates, however this success has also led to a higher prevalence of conditions associated with premature birth, such as ROP.[2,3] This disease is characterized by abnormal development of the retinal vasculatures and has the potential of commencing severe and irreversible visual loss if left untreated.[4,5] Although data on the incidence and severity of retinopathy of prematurity (ROP) in Bangladesh are limited, several small-scale hospital-based studies have reported incidence rates ranging from 4.4% to 40%.[6–8]

Treatment for ROP includes laser photocoagulation, anti-VEGF therapy, and, in severe cases, surgery.[9] Laser photocoagulation ablates the peripheral avascular retina to prevent further detachment. Anti-VEGF injections, such as Ranibizumab or Bevacizumab, inhibit VEGF to reduce abnormal vessel growth. In advanced cases with retinal detachment, surgeries like scleral buckling or vitrectomy may be required to preserve vision. However, successful management of ROP depends not only on the initial intervention but also on regular monitoring. These follow-ups are crucial for tracking the prognosis, administering additional treatments as necessary, and preventing severe complications. Despite the effectiveness of treatments, ROP can still reoccur or progress. In many cases, the peripheral retina remains avascular, posing a risk for

reactivation of abnormal vascular growth. While effective in suppressing abnormal vessels, anti-VEGF therapies may require repeat treatments because VEGF levels can rise again as the eye grows, leading to reactivation of neovascularization. Moreover, along with the natural development of the eye, the immature retina can still pose risk of progression. While laser treatment reduces the risk by ablating the peripheral retina, it may not fully prevent future retinal detachment or fibrosis. Additionally, long-term complications such as scarring and retinal traction can develop over time, potentially leading to retinal detachment even after successful initial treatment. Studies have shown that up to 25% of infants experience reactivated ROP requiring further treatment.[10] Repeated intravitreal injections or laser treatments are often required to manage reactivated ROP. [11] However, the risk of reactivation remains significant, necessitating careful and ongoing monitoring to ensure timely intervention and prevent further disease progression.[12] Regular follow-up facilitates early detection of such issues, significantly reduces the risk of severe visual impairment.[13]

Ensuring treatment compliance and consistent follow-up care remains a significant challenge for caregivers, impacting the effectiveness of intervention, that can lead to disease progression and permanent vision loss, exacerbating the burden on healthcare systems and affected families. Factors such as adhering to follow-up treatments for neonates in Bangladesh, particularly for conditions like ROP is challenging. Inadequate healthcare infrastructure, particularly in rural areas, creates significant barriers for families seeking specialized medical care, often necessitating long and costly journeys to urban centers. This not only places a financial and emotional strain on families but also disrupts their ability to maintain consistent follow-ups, thereby impacting long-term treatment outcomes and the overall effectiveness of healthcare interventions. Financial constraints, lack of awareness about the importance of follow-up appointments and communication difficulties between caregivers and healthcare providers contribute to poor adherence to scheduled follow-ups.

In the present research, the rate of compliance with follow-up visits among ROP infants in Bangladesh have been investigated along with evaluating the most frequently occurring stages of ROP and assess the efficacy of treatments with the aim of guiding policy development, and enhance healthcare strategies, ultimately improving health outcomes for vulnerable preterm infants.

2. OBJECTIVE

Primary objective: To assess the rate of follow-up visits among the post injection and post laser infants in ROP in our center.

Secondary objective: To assess the distribution of different stages of ROP.

3. METHODOLOGY

Subjects and Methods: This retrospective observational study was conducted at Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The study period spanned from January 2021 to December 2023. Infants with gestational age ≤35 weeks and/or birth weight ≤2000 gm were screened for ROP. The study included infants who were diagnosed with ROP and subsequently required one or more of the following treatments:

- Intravitreal anti-VEGF (Avastin) injection,
- Laser photocoagulation therapy,
- A combination of both intravitreal injection and laser therapy
- Surgical intervention

Infants who did not require treatment for ROP or were lost to follow-up before receiving any intervention were excluded.

Data Collection: Medical reports were accessed and reviewed to collect data on ROP diagnosis, follow-up compliance and treatment outcomes. The follow-up schedule for each infant was standardized according to the treatment modality received: 1st, 2nd, 4th, 8th and 12th week for laser photocoagulation; 1st or 2nd day, 1st, 2nd, 4th, 8th, 12th and 16th week for intravitreal anti-VEGF injection. The rate of compliance to follow-up visits was recorded at each of these intervals.

Variables: The primary variable of interest was the compliance rate to scheduled follow-up visits, which was calculated as the percentage of infants who attended each scheduled visit.

Secondary variables included:

- The stage and severity of ROP at the time of diagnosis (based on the International Classification of Retinopathy of Prematurity),
- Treatment modalities used (injection, laser, or combination),
- Need for rescue laser treatment post-intravitreal anti-VEGF injection,

Data Analysis: Descriptive statistics were used to summarize the demographic data, such as gestational age and birth weight of the infants. The results were reported as frequency, percentages, means, and standard deviations where applicable. Statistical analysis of the results was done by using IBM-SPSS software version 25 (SPSS Inc, Chicago, IL, USA).

Ethical consideration: Institutional review board (IRB) sanction was availed from hospital ethical committees before accessing and reviewing medical records. Patient confidentiality was strictly maintained by de-identifying and anonymizing all collected data.

4. RESULT

This study examined the medical records of 2,207 newborns, of which 950 met the eligibility criteria for ROP screening. Finally, a total 295 newborns had ROP who required and received treatment. In this sample, 50 cases of ROP were identified among 155 newborns (32.26%) in 2021, 118 cases among 392 newborns (30.10%) in 2022, and 127 cases among 403 newborns (31.51%) in 2023 (Table I).

Table I: Distribution of the sample according to the yearly incidence of ROP (N=950)

Year	Total no screening	Incidence of ROP	Incidence Rate
2021	155	50	32.26%
2022	392	118	30.10%
2023	403	127	31.51%
Total	950	295	31.05%

Within a range of 28.00 - 38.00 weeks, the mean gestational age of the sample was 33.39 weeks. The birth weight of the sample ranged from 700 - 3000 gm with the mean birth weight of 1795.41 gm (Table II).

Table II: Mean Gestational age and birth weight of the sample (N=295)

	Mean	Range
Gestational age	33.39 weeks	28.00 - 38.00 weeks
Birth Weight	1795.41 gm	700 - 3000 gm

The data in Table III presents the distribution of ROP cases based on diagnosis stages over three years. Aggressive ROP (A-ROP) had the highest occurrence, with 130 cases (44.07%) during this time, showing a steady increase across the years: 13 cases in 2021, 54 in 2022, and 63 in 2023. Stage 3 (Zone II and III) accounted for 50 cases (16.95%), with a relatively stable distribution over the years: 11 cases in 2021, 18 in 2022, and 21 in 2023. Stage 1 and 2 was the second most common diagnosis, comprising 92 cases (31.19%). The distribution remained fairly consistent across the years: 25 cases in 2021, 32 in 2022, and 35 in 2023. Stage 4 showed a notable increase over time, with only 1 case in 2021, 4 cases in 2022, and a significant rise to 14 cases in 2023, totaling 19 cases (6.44%). Stage 5, the most severe stage, comprised 14 cases (4.75%). It also showed a rising trend, with 1 case in 2021, 5 in 2022, and 8 in 2023.

Table III: Sample distribution based on diagnosis (N=295)

Diagnosis	2021	2022	2023	Total
	(n=50)	(n=118)	(n=127)	(N=295)
A-ROP	13	54	63	130 (44.07%)
Stage 3 Zone II and III	11	18	21	50 (16.95%)
Stage 1 and 2	25	32	35	92 (31.19%)
Stage 4 (A+B) ROP	1	4	14	19 (6.44%)
Stage 5	1	5	8	14 (4.75%)

The data on treatment modalities for ROP shows that anti-VEGF injections were the most frequently used intervention, applied in 43.05% of cases, followed closely by laser treatment at 40.00%. A smaller portion of cases, 14.58%, required a combination of injection and laser therapy, indicating a need for more intensive treatment in certain instances. Surgical intervention was necessary in 9.15% of cases. Additionally, rescue laser treatment was used in 14.58% of cases (Table IV).

Table IV: Sample distribution based on treatment (N=295)				
	2021	2022	2023	Total
	(n=50)	(n=118)	(n=127)	(N=295)
Injection	10	54	63	127 (43.05%)
Laser	29	42	47	118 (40.00%)
Injection + Laser	10	13	20	43 (14.58%)
Surgical Intervention	1	9	17	27 (9.15%)
Rescue laser	10	13	20	43 (14.58%)

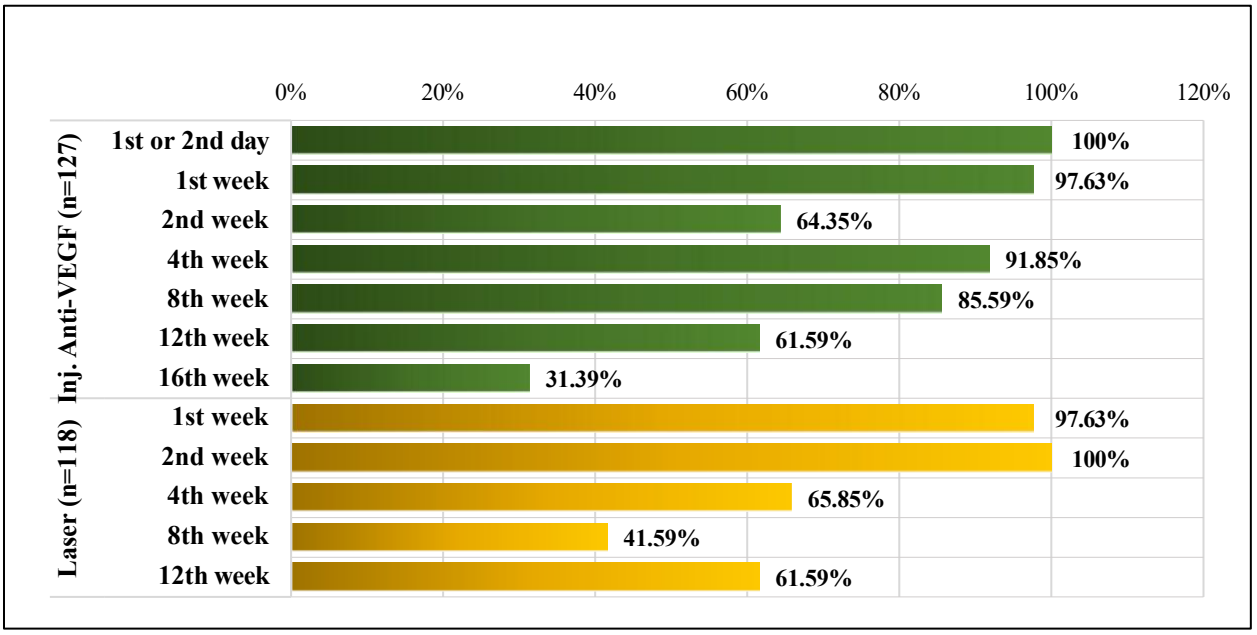

Figure I: Post-treatment follow-up schedule and compliance (N=245)

Figure 1 demonstrates the post-treatment follow-up schedule and compliance of the anti-VEGF injections and laser treatment. It reveals that both the treatments exhibit high initial compliance, with 100% attendance for anti-VEGF injections in the first 1-2 days and full compliance for laser treatment by the 2nd week. However, follow-up compliance showed a marked decline over time. Follow-up visits dropped to 61.59% in both treatment modality groups at 12th week.

DISCUSSION

The global trends in ROP reveal a contrasting scenario, with its incidence decreasing in developed countries.[14] However, in Bangladesh, the prevalence of ROP has notably increased over the years.[15,16] This rise can be attributed to a combination of factors, including improved survival rates of preterm infants, which increase the at-risk population, inadequate neonatal care facilities, and the absence of widespread screening programs.[17] While medical advancements have helped reduce ROP in high- resource settings, the limited access to specialized neonatal care and timely intervention in developing countries like Bangladesh contributes to the ongoing challenge of managing and preventing ROP. In this study, the prevalence of ROP among eligible newborns was consistent across the years, with 32.26% in 2021, 30.10% in 2022, and 31.51% in 2023 with an average of 31.05%. In a study in India a comparable prevalence have been found with 29.57%.[18]

This study observed a concerning trend, with a higher incidence of more severe stages of the disease. A-ROP was the most common diagnosis, accounting for 44.07% of cases. Development of severe forms of ROP, such as A-ROP can be attributed by the increasing survival rates of extremely preterm infants. For example, studies reporting that 75% of infants born between 28-30 weeks develop ROP.[19] The higher prevalence of A-ROP could also be influenced by factors such as neonatal care practices, oxygen therapy protocols, and early intervention strategies. However, the mean gestational age of affected infants was 33.39 weeks, and their mean birth weight was 1795.41 grams. Consistent with these findings, recent studies have

indicated that A-ROP can also be observed in infants who are larger and less preterm.[20–22] Among other clinical presentation of ROP, stage 1 and 2 were the second most common diagnoses, representing 31.19%. Stage 3 ROP (Zone II and III) accounted for 16.95% of cases, while stage 4 ROP made up 6.44% of cases, and stage 5, the most severe stage, comprised 4.75%. In a study in Bangladesh, Rahman et al. observed similar observation, with 35% of cases in stage 1, 35% in stage 2 and majority of cases (50%) were located in Zone 3.[19] In another study in Bangladesh, Nahar et al. found that stages 1 and 2 accounted for 45% of ROP cases, while stage 3 represented 23%, stage 4 comprised 5%, and stage 5 made up 9%. Additionally, aggressive posterior ROP was observed in 18% of all cases in their study.[23]

The current approach to treat ROP primarily involves the application of anti-VEGF injections and laser treatment as the most common intervention.[5,24] Similarly, in this study anti-VEGF injections were the most common intervention, used in 43.05% of cases, followed by laser treatment at 40.00%. In this study sample, a combination of Anti-VEGF injection and laser therapy was required in 14.58% of cases. This approach is supported by its potential advantages, including the need for a lower dose of Anti-VEGF, reduced recurrence compared to monotherapy, and preservation of the central visual field.[25] These benefits make it a preferred option for managing severe cases of ROP, as it enhances both rapid disease regression and peripheral retinal vessel development, consistent with evidence supporting this combined approach as an effective modality for treating severe ROP.[26] Surgery was necessary in 9.15% of the cases. Rescue laser treatment was also employed in 14.58% of cases. In comparison, previous large scale studies have reported the need for rescue treatments in 25–30% of infants with treated ROP.[27,28] The lower rate of requirement for rescue treatment in this study may have been consequent from the higher rate of discontinuation in long-term follow-up.

Compliance with treatment is a critical factor influencing outcomes in ROP management. Follow-up adherence ensures that the immediate therapeutic goals are met, setting the foundation for better long-term outcomes. Both anti-VEGF injections and laser treatments demonstrated high initial follow-up compliance in this sample, but adherence declined significantly over time. Laser and anti-VEGF injection follow-up compliance both were similar at the 12th week follow-up (approximately 62%). However, Anti-VEGF injection follow-up compliance fell sharply to 31.39% by the 16th week, indicating substantial challenges in maintaining long-term adherence. In this sample, several key initiatives and practices have been implemented to enhance the management as well as to increase post-treatment follow-up of ROP. The establishment of the ROP center by BSMMU in collaboration with ORBIS International marks a significant step in providing specialized care. Since January 2020, the procurement of Trinethra has been a critical component, facilitating advanced treatment options. Efforts to enhance follow-up rates for ROP have been supported by other interventional studies, which demonstrated that follow-up compliance significantly improved with the introduction of newly designed patient educational materials that adhere to health literacy guidelines.[29] Similarly, efforts to educate parents about the severity of ROP have been reinforced through comprehensive documentation, learning sessions, and personalized counseling. These initiatives aim to enhance parental understanding and engagement in follow-up care, which are crucial for the successful follow-up compliance of ROP. Communication strategies include regular contact with parents via mobile phones and interactions with other family members to ensure a supportive network. Regarding treatment costs, Anti-VEGF injections are priced at Taka 3000 for both eyes, while laser treatment costs Taka 6000 for both eyes, with no additional charges for follow-up sessions. This cost structure may have contributed to greater adherence to treatment and follow-up care, reducing the financial burden on families and potentially improving long-term outcomes for affected infants. Simultaneous findings have been reported previously. Drawing evidences from successful models like the KIDROP program, where, weekly imaging until a postmenstrual age of 44 weeks, fortnightly until 52 weeks, and monthly thereafter helped to prevent loss to follow-up and allow for early intervention when vascularization growth or recurrence is detected, especially in infants who require long-distance travel for treatment.[30] In other observation, it has been suggested that, cases where compliance to follow-up diminishes or there is evidence of active flat neovascularization, laser treatment should be considered which have been implemented in this study.[31]

5. CONCLUSION

The findings of this study emphasize the critical need for ongoing vigilance in the screening, management, and post-treatment follow-up of ROP. This is particularly important given the rising incidence of severe ROP and the necessity for further intervention after initial treatment witnessed in this study. Despite high initial compliance, long-term follow-up remained challenging in this sample, highlighting the need for enhanced strategies to maintain adherence and effectively manage ROP over time.

6. RECOMMENDATION

Future studies should explore the factors contributing to poor compliance and follow-up after ROP treatment, with the goal of identifying high-risk groups prone to loss of follow-up. This will enable the development of targeted intervention and counseling strategies aimed at improving compliance and ensuring consistent follow-up care. Understanding the factors that contribute to non-compliance is crucial to improving long-term outcomes for ROP patients in resource-limited settings.

Data Availability: The data are available upon request from the corresponding author.

Conflict of Interest: The authors declare that they have no conflicts of interest related to this study.

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