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Research Article

EVALUATION OF CLINICAL COURSE AND OUTCOMES IN ZONE I RETINOPATHY OF PREMATURITY IN A TERTIARY CARE INSTITUTE

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ABSTRACT

Objectives: The objectives are to study the clinical course and outcomes of Zone I retinopathy of prematurity and also to study the indication of management and the factors affecting the choice of treatment modality.

Methods: The present study was a prospective observational study conducted at the Department of Ophthalmology. All the neonates having Zone I retinopathy of prematurity (ROP) at presentation according to the International Classification of ROP classification were included in the study after obtaining permission from the institutional ethics committee and consent from parents.

Results: In the present study, 526 neonates were screened and ROP was detected in 131 neonates with an incidence of 24.90%. Out of those 131, Zone I ROP was detected in 50 neonates, giving an incidence of 9.50%.

Conclusion: In our study, Type 1 ROP has a variable course with 47.61% who initially had mild-looking disease developed Type 1 ROP requiring treatment. Hence, a proper timely follow-up is also important in these patients, we cannot exclude the probability of ROP based on the first examination, because when they are present, they are very preterm so vascularization is only until Zone I.

Keywords: Zone 1 retinopathy, Retina, Retinopathy of prematurity, Neonates.

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INTRODUCTION

India has the highest number of premature births in the world [1]. Developing countries including India have an incidence of retinopathy of prematurity (ROP) ranging from 38% to 47% in different regions of India [1-3]. ROP is a disorder of the development of retinal blood vessels in premature infants. Normally retinal vascularization starts from the optic disc to the ora serrata. Vascularization up to nasal ora serrata was completed by 8 months of gestation and temporal ora by 10 months of gestation. This is why a peripheral avascular retina exists in a premature infant [4,5]. At present, India with other developing countries is facing the "third epidemic" of ROP due to many factors, such as increased survival of preterm babies, inadequate quality of neonatal care, and low coverage of screening and treatment services for ROP. Zone I ROP is a severe form of the disease and accounts from 10% to as high as 35% of all treated ROP cases [6]. Zone I ROP is characterized by the rapid progression of the disease from stages 1 to 3 within a matter of days and has a tendency to progress to retinal detachment with extremely poor visual outcomes if not treated timely. Out of three zones, Zone I ROP is the most aggressive one as it is the most important area in aspects of vision and vascularization is so immature [7]. In Zone II and Zone III, clinical course and treatment outcomes are predictable as most of the research is available. The real challenge is posed by Zone I ROP in which vascularization is so immature that laser landmarks are yet to appear and anti-vascular endothelial growth factor (anti-VEGF) is still questionable as far as safety and end points are concerned. In India, laser or anti-VEGF therapy is available only at tertiary care centers so most of the time is wasted on referrals and it progresses very rapidly [8]. Outcomes were favorable with early intervention in the forms of laser and intravitreal anti-VEGF agents, reducing the need for surgical intervention. Hence, the present study was done to study the clinical course and outcomes of Zone I ROP and also to study the indication of management and the factors affecting the choice of treatment modality.

METHODS

The present study was a prospective observational study conducted at the Department of Ophthalmology, Gandhi Medical College, and Hamidia Hospital, Bhopal. All the neonates having Zone I ROP at presentation according to the International Classification of ROP (ICROP) Classification were included in the study after obtaining permission from the institutional ethics committee and consent from parents. Initial ocular examination was carried out in diffuse light with the help of a torch, and the following things were noted such as persistent hyperplastic primary vitreous, persistent pupillary membrane, rubeosis iridis, pupillary reaction, or any other anterior segment pathology. One drop of 5% phenylephrine and 0.8% tropicamide was instilled to dilate the pupil in intervals of 15 min for 2–3 times. The zone of vascularization (from I to III), presence or absence of plus or preplus disease, and the stage of ROP were evaluated as per ICROP. In cases where ROP is detected, fundus photo-documentation is done using 3nethra NeoCam for future reference and to detect the progression or regression of ROP either spontaneously or following treatment. Any patient who comes under Zone I ROP was divided into two groups: Type 1 ROP requiring treatment and Type 2 ROP not requiring treatment. These two groups were observed till the completion of vascularization, regression of ROP, and progression despite adequate medical and laser treatment. Follow-up was done as per the early treatment for ROP (ETROP) schedule and parents were counseled regarding the importance of timely follow-up for early detection of ROP and intervention. Based on ETROP guidelines, laser treatment was recommended for Type 1 ROP, anti-VEGF treatment for stage 3 ROP with plus disease in Zone I, and vitrectomy or vitreoretinal surgery for stages four and five in Zone I disease.

Statistical analysis

Data were collected and entered simultaneously in Statistical Package for Social Sciences version 23 and coded appropriately. The data

Table 1: Staging of Zone I ROP at presentation

Stage	Frequency (n=97)	Percentage
Stage 1	52	53.60
Stage 2	21	21.64
Stage 3	16	16.49
APROP/AROP	8	8.24
Total	97	100

ROP: Retinopathy of prematurity, APROP: Aggressive posterior retinopathy of prematurity, AROP: Aggressive retinopathy of prematurity

Table 2: Characteristics of Zone I ROP based on the presence of plus/preplus disease at presentation

Eyes having plus/ preplus disease	No. of eyes	Percentage (n=97)
Plus disease	20	20.61
Preplus disease	18	18.55
No plus/preplus	59	60.82
Total	97	100

ROP: Retinopathy of prematurity

were analyzed keeping in view the aims and objectives of the study. Descriptive statistics were calculated to summarize the sample characteristics in terms of frequency and percentage. Graphs and charts were made. Analytical and inferential analysis was applied between the dependent variable and other independent variables. Significance was set at standard 0.05.

RESULTS

In the present study, 526 neonates were screened and ROP was detected in 131 neonates with an incidence of 24.90%. Out of those 131, Zone 1 ROP was detected in 50 neonates, giving an incidence of 9.50%. According to staging in the Zone I ROP at the first presentation, it was found that 52 (53.60%) eyes had stage 1, 21 (21.64%) eyes had stage 2, 16 (16.49%) eyes had stage 3, and 8 (8.24%) eyes of four patients had bilateral aggressive posterior ROP (APROP)/aggressive ROP (AROP). The majority of patients had stage 1 disease. Furthermore, 59 (60.82%) eyes had no plus or preplus disease, 20 (20.61%) eyes had plus disease, and 18 (18.55%) eyes had the preplus disease. It was found that 25 eyes with stage 1 and 1 eye with stage 2 had spontaneous regression and 6 eyes with stage 1 and 1 eye with stage 2 had progression then spontaneous regression. A total of 60 eyes had progression then regression after treatment of which 21 had stage 1, 19 had stage 2, 14 had stage 3, and 4 eyes had progression even after treatment which 2 eyes had stage 3 and 2 eyes had APROP. The clinical course of Type 1 Zone I ROP at presentation total of 34 eyes presented as Type 1 ROP no eye presented with stage 1 plus disease, and 10 eyes presented with stage 2 plus disease treatment was given and regression was seen in all of them. A total of 16 eyes were presented as stage 3 and treatment was given out of which 14 eyes showed regression after treatment and 2 eyes of 1 infant showed progression even after treatment. A total of 8 eyes of 4 infants presented as APROP/AROP and treatment was given out of which 6 eyes of 3 infants showed regression and 2 eyes of preterm showed progression. In the clinical course of Zone I Type 2 ROP, a total of 63 eyes presented with Type 2 ROP on follow-up out of which 30 eyes showed progression and converted into Type 1 ROP and the rest 33 eyes remained as Type 2 ROP and spontaneous regression was seen. Out of 30 eyes that are converted into Type 1, 21 eyes of Stage 1 show progression with 12 eyes in Stage 2 plus and 9 eyes progressing in Stage 3. Out of 30 eyes that are converted into Type 1, 9 eyes of stage 2 progress to stage 3 and show regression after treatment. Out of 97 eyes of 50 neonates with ROP, there were 54 eyes in which laser treatment was given and 10 eyes had given anti-VEGF followed by laser therapy as treatment. Out of 54 eyes given laser therapy, 52 eyes (96.29%) show favorable outcomes and 2 eyes (3.70%) show the progression of the disease and refer to a higher center. Out of 10 eyes given anti-VEGF followed by laser therapy, 8 eyes (80%) showed favorable outcomes

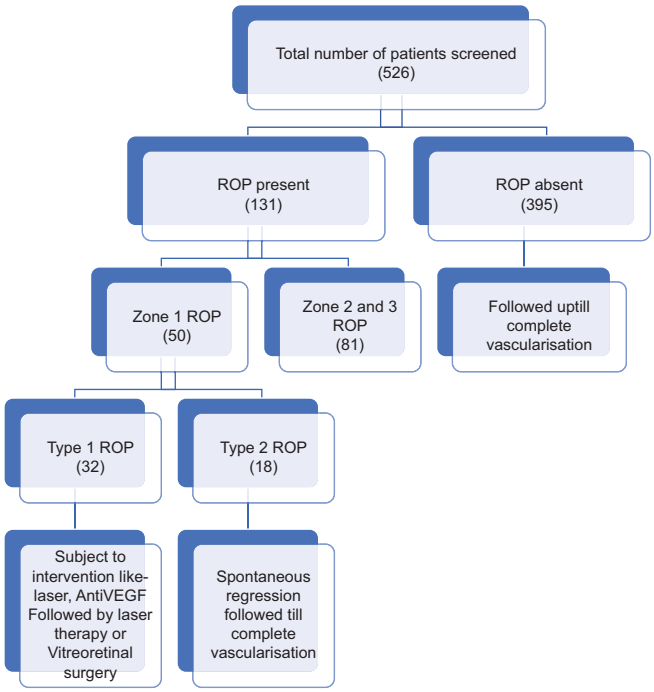

Fig. 1: Flowchart showing total no. of patients screened and ROP present or absent

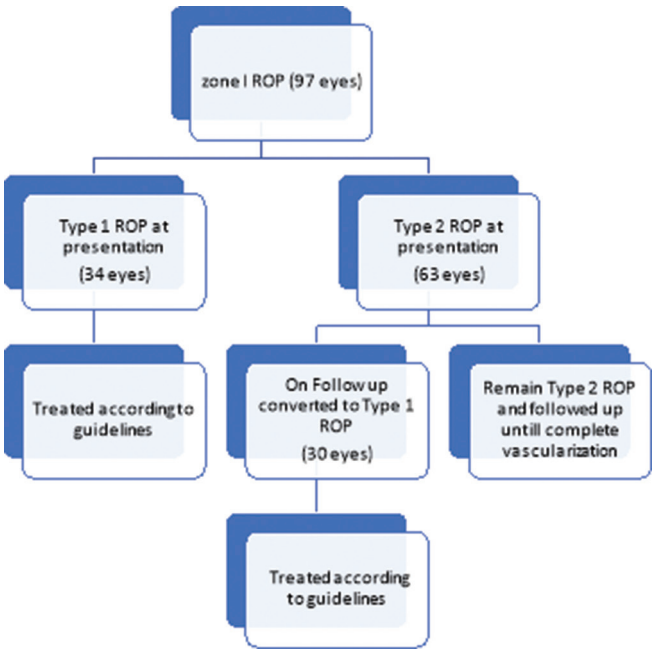

Fig. 2: Flowchart showing patients having Zone I ROP disease which further divided according to type 1 and type 2 and there follow up

and 2 eyes (20%) showed progression of the disease and were referred to a higher center (Tables 1-6).

DISCUSSION

In the present study, 526 infants were screened and showed an institutional incidence of ROP of 24.9% (131 out of 526 infants) and Zone I ROP of 9.5% (50 infants). Much lower incidences of 1.8% and 3.7% were reported by Braimah *et al.* [9] (Ghana) and Fekri *et al.* [10] (Iran). The wide variation between the incidence of Zone I ROP between the present study and other Western studies is attributable to the variation in the sample size of the studies and

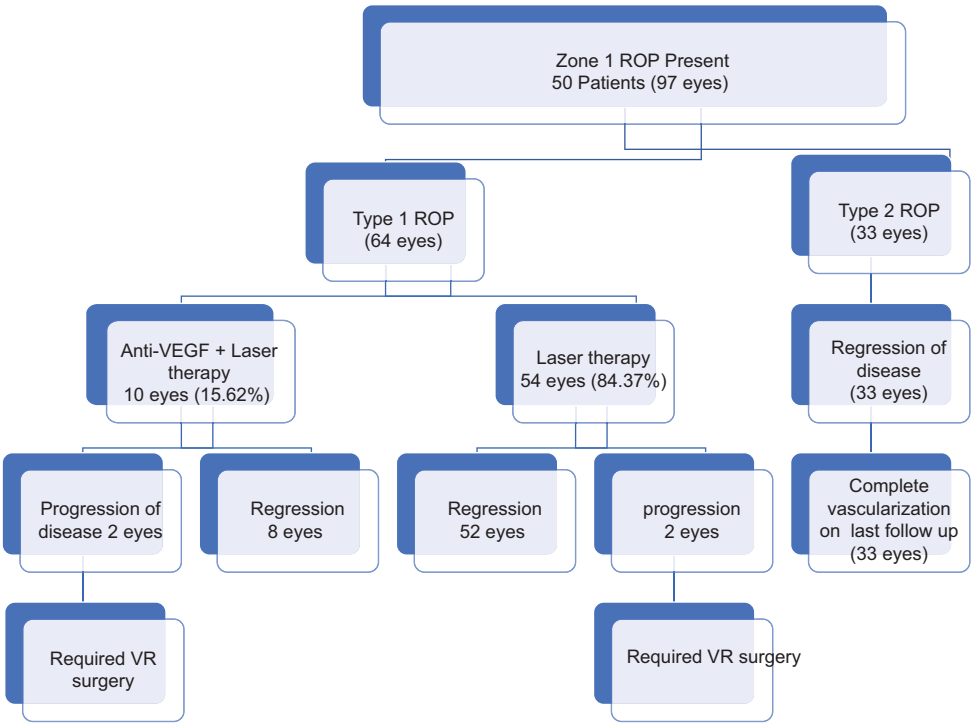

Fig. 3: Flow chart showing treatment outcome of type 1 and type 2 ROP (after antiVEGF ranibizumab,laser therapy or both) and showing regression or progression

Table 3: Clinical course of Zone I ROP stagewise

Stage	Spontaneous regression	Progression then regression	Progression then regression after treatment	Progression even after treatment
Stage 1	25	6	21	-
Stage 2	1	1	19	-
Stage 3	-	-	14	2
Stage 4	-	-	-	-
Stage 5	-	-	-	-
APROP/AROP	-	-	6	2
Total	26	7	60	4

ROP: Retinopathy of prematurity, APROP: Aggressive posterior retinopathy of prematurity, AROP: Aggressive retinopathy of prematurity

Table 4: Clinical course of Zone I Type 1 ROP (n=30) at presentation

Stage	Regression on treatment	Progression despite treatment	Total
Stage 1 plus	-	-	00
Stage 2 plus	10	-	10
Stage 3	14	2	16
APROP/AROP	6	2	08
Total	30	4	34

ROP: Retinopathy of prematurity, APROP: Aggressive posterior retinopathy of prematurity, AROP: Aggressive retinopathy of prematurity

Table 5: Clinical course of Zone I Type 2 ROP at presentation

Stage	Progresses to type 1	Regression
Stage 1	21	31
Stage 2	9	2
Stage 3	-	-
Total	30	33

ROP: Retinopathy of prematurity

Table 6: Distribution of eyes according to outcome

Patient outcome	Eyes (n=64)	Percentage
Favorable outcome		
Anti-VEGF followed by laser therapy	8 (80)	93.75
Laser therapy	52 (96.29)	
Nonfavorable outcome		
Anti-VEGF followed by laser therapy	2 (20)	6.25
Laser therapy	2 (3.70)	

Anti-VEGF: Anti-vascular endothelial growth factor

the difference in inclusion and exclusion criteria of the studies. In an Indian study conducted by Patel *et al*. [11], all newborns at a tertiary care hospital in Vadodara 8.7% developed Zone I ROP which is similar to our study.

In our study, according to staging in Zone I at the first presentation 52 (53.60%), 21 (21.64%), 16 (16.49%), and 8 (8.24%) eyes had stage 1, stage 2, stage 3, and APROP/AROP respectively. Out of these three neonates have unilateral involvement with stage 1 others had bilateral involvement. Four infants had bilateral APROP/AROP. Of these 20.61% of neonates had the plus disease at presentation. According to Sen *et al*. [6], out of 78 eyes, 10.25% were categorized as stage 1, 1.28% as stage 2, 17.94% as stage 3, 35.89% as stage 4, and 34.61% had stage 5. Plus disease was presented in 50% of the cases.

In our study, we found that out of 97 eyes, a total of 33 (34.02%) eyes show spontaneous regression all of them belong to stages 1 and

2. 64 (65.97%) eyes required treatment out of which 60 (61.85%) regressed after treatment and 4 (4.12%) eyes show progression despite treatment. Of those four eyes, two had stage three plus disease and two had APROP. This shows that in Zone I disease was aggressive and required prompt treatment. Favorable outcome was seen in most of the neonates. According to Sen *et al*. [6], out of 78 eyes 60 eyes (77%) required treatment. According to Prost [12], 6% of cases in the Zone I showed spontaneous regression. According to Wang *et al*. [13], found no ROP in Zone I that spontaneously regressed in 237 individuals. In our study out of 9nall eyes 34 (35.05%) eyes presented as Type 1 ROP in Zone I and 63 (64.94%) eyes as Type 2 ROP. On further follow-up 30 (47.61%) eyes converted into Type 1 ROP and required treatment and 33 remain as Type 2 later on regression is seen and complete vascularization is seen on the last follow-up. In our study Type 1 ROP has variable course and outcome. Many of the patients who look innocuous at presentation developed serious diseases afterward. Of those who had mild-looking disease of them, 47.61% showed progression and required treatment. Our study demonstrated anatomical outcomes following treatment in 97 eyes presenting with any stage of ROP with Zone I disease. Out of 97 eyes of 50 infants with Zone I ROP, 34 (35.05%) eyes presented as Type 1 ROP, and 63 (64.94%) eyes were as Type 2 ROP. On further follow-up of Type 2 ROP, 30 (47.61%) eyes converted into Type 1 ROP and required treatment and 33 remained as Type 2 later on regression is seen and complete vascularization is seen on the last follow-up.

Hence, a total of 64 eyes required treatment, 54 eyes (84.37%) received laser therapy and 10 eyes (15.62%) received anti-VEGF followed by laser therapy as treatment. A favorable outcome is seen in 93.75% and a nonfavorable outcome is seen in 6.25%. A total of four eyes showed nonfavorable outcomes out of them 2 eyes of 1 infant had stage 3 plus disease in both eyes which received laser therapy, and 2 eyes of 1 infant had APROP which received anti-VEGF followed by laser therapy. As both infants had severe diseases. Favorable outcome was seen in stage 1 (100%), stage 2 (100%), stage 3 (87.5%), and APROP (75%). According to Karkhaneh *et al.* [14] out of 65 eyes with Zone I ROP, 82.9% regressed after a single intravitreal bevacizumab (IVB) injection, and 12 eyes (17.1%) needed reinjection. Overall, 92.9% of eyes had favorable structural outcomes after one or two injections of IVB. Five eyes (7.1%) progressed to retinal detachment and required surgical management. Katoch *et al.* [15] studied treatment outcomes in posterior Zone I ROP where five of six (83.3%) eyes receiving combined treatment with IVB followed by laser photocoagulation had favorable outcomes whereas only 7 of 50 (14%) eyes treated with laser monotherapy had a favorable outcome.

CONCLUSION

ROP is a retinal vascular disease, occurring exclusively in premature infants of low birth weight and those who often have been exposed to a high concentration of oxygen. Zone I ROP is a severe form of the disease, because of the rapid progression of the disease and tends to progress to retinal detachment with poor visual outcomes if not treated promptly. In our study Type 1 ROP has variable course with 47.61% who initially had mild looking disease developed Type 1 ROP requiring treatment. Hence, a proper timely follow-up is also important in these patients, we cannot exclude the probability of ROP based on the first examination, because when they are present, they are very preterm so vascularization is only until Zone I. Hence, the fade of this vascularization can be toward the development of Type 1 ROP.

A favorable outcome is seen in 93.75% and a nonfavorable outcome is seen in 6.25% after treatment. APROP/AROP is a severe disease spite of that 75% had favorable outcomes after treatment, this shows timely intervention with newer modalities can save these eyes.

LIMITATIONS AND SCOPE

Our study's strongest point is that it covers the complete range of Zone I ROP. In this study, a treatment strategy for Zone I ROP in a tertiary care facility where infants may be admitted late and at varying degrees of severity is shown. A quick multifaceted strategy is required in this situation to treat these infants and prevent the unfavorable consequences of total blindness.

More research should be done in this direction to identify the factors that are protective toward the development of Zone I ROP. A study with a larger sample size is required for better predictability of such factors. This was a hospital-based prospective study, larger studies are required to investigate these associations further.

ETHICAL APPROVAL

Approved.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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