

Structural Outcome of Treated Retinopathy of Prematurity Patients

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Abstract

Purpose: To evaluate the structural outcomes of treated neonates with retinopathy of prematurity (ROP)

Methods: In this cross-sectional study from April 2008 to August 2009, 859 patients were investigated. These neonates had been consulted at the retinal clinic of Farabi Eye Hospital of Tehran University of Medical Sciences. Those with gestational age of no more than 36 weeks and birth weight of below 2,500 g were enrolled to the study. According to the fundoscopic examination of patients, laser treatment alone or with scleral buckle or Avastin, vitrectomy and/or scleral buckle were performed. Treatments were done by two surgeons with one protocol. Indirect laser therapy was performed for threshold and pre-threshold status. In stage 4 when anterior, posterior traction was seen we performed vitrectomy, and when peripheral traction or retrolental fibroplasia was seen scleral buckling was applied. In stage 5 when exudative retinal detachment was observed scleral buckling was performed and in the case of tractional retinal detachment vitrectomy was performed.

Results: Study commenced with 734 eyes [405 males (55%) and 329 females (45%)] with ROP. From the total number of 734 eyes, treatment was found necessary for 327 eyes (44%). Among the above mentioned 327 eyes, 231 eyes (70%) were treated by diode laser photocoagulation in which laser treatment was applied in stage 2, stage 3, stage 4A in 90 eyes (38%), 132 eyes (56%), 19 eyes (8.2%), respectively. In 202 eyes (84%) ROP regressed. Univariete analysis showed a significant relation between gestational age ($P<0.0000$), age of first examination ($P<0.001$), age of referral ($P=0.000$), respiratory distress syndrome (RDS) ($P=0.02$), duration of oxygen therapy ($P=0.01$), weight ($P=0.000$) and patients needed treatment. Univariete analysis showed a significant relation between gestational age, age of first examination, age of referral, weight, duration of oxygen and ventilation application, RDS, intraventricular hemorrhage (IVH), sepsis and ROP. In a logistic regression analysis the gestational age, weight, RDS, duration of oxygen therapy were significantly associated with ROP. In a logistic regression analysis regression after laser treatment were significantly associated with risk factors such as gestational age, age at the first referral, birth weight, RDS. In a logistic regression analysis attachment after treatment were significantly associated with gestational age at first examination. Favorable structural outcomes of 84% were occurred in patients treated with laser.

Conclusion: Laser photocoagulation resulted in more anatomical success in prethreshold ROP compared with threshold ROP. We had more favorable outcomes in laser treated patients in stage 2 and 3. Vitrectomy resulted in more anatomical success than scleral buckling. Systemic factors had significant effect on the anatomical outcome.

Keywords: Retinopathy of Prematurity, Structural Outcome, Prethreshold, Threshold, Laser

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Introduction

One of the main causes of childhood blindness in developed and developing countries, is retinopathy of prematurity (ROP).¹ ROP causes the normal development of the retina to be stalled and the vessels begin to develop in the abnormal pattern of angiogenesis and multiplication of the tissues of the retina.²

This disease is a great challenge for all physicians who are dealing with the premature infants.³ There are about 50,000 cases of blindness reported annually worldwide.⁴ In USA, annually there are about 1,300 infants reported with impaired vision due to ROP, out of which about 250 to 500 have severely damaged eye sight. Out of every one million, 300 infants are reported to become blind due to this disease in at least one eye.⁴ Studies in Europe suggest that about 6% to 17% of blindness in infants is because of ROP.

In Philippine and Thailand investigation prove that about 15% of the urban infant blindness is due to ROP. Another research done in South Africa suggests that 10.6% of infant blindness is due to ROP.^{5,6} This disease if detected at an early stage can be cured and will respond favorably to treatment, in case of delay in a short span of time it will lead to blindness, thus there have been different methods classified for timely identification and treatment of retinopathy of prematurity. Different studies have shown that regular follow-up of the patients, increase in the knowledge and awareness of the intensive care unit staff, and timely treatment with laser can help reduce the effects of the disease and reduce blindness.⁷⁻¹⁰

According to the study done by Jalali and colleagues on ROP in 2003, at the present, following are the advised treatments for ROP. In case of threshold and prethreshold level of ROP laser or freezing is recommended. Surgery with scleral buckling and the vitrectomy is recommended in stages IV and V.¹¹

Different studies showed that genetics and race can have an effect on occurrence of the ROP¹²⁻¹⁵ and may have effect on outcome. Therefore this study was conducted to identify the outcome of treatments done for ROP patients in Farabi Eye Hospital, as an example of a tertiary care center, which is a good representative of the Iranian population.

The anatomical success rates are different in different studies, for example the success rate in prethreshold, threshold ROP has been reported to be 80.3% to 96.5%^{16,17} and in stage 4 from 14% to 90%^{18,19} and in stage 5 from (0-50) has been reported.

Methods

Premature infants with birth weight less than 2,500 grams, having less than 36 weeks of gestational age, were included in our study. All infants were screened for ROP from April 2008 to March 2009. All preterm infants underwent complete ophthalmologic examination using indirect ophthalmoscopy by lens +20 or 30 D. The patients' retinas were inspected and based on the retinal situation, the follow-up or the need for treatment was decided. Laser treatments were done for the prethreshold type (zone 1, any stage, plus; zone 1, stage 3, without plus; zone 2, stage 2 or 3, plus) or threshold status. In stage 4 when anterior, posterior traction was seen we performed vitrectomy, and when peripheral traction or retrolental fibroplasias was seen, scleral buckling was done. In stage 5 when exudative retinal detachment was observed scleral buckling was performed and in the case of tractional retinal detachment vitrectomy was performed. They were either treated with scleral buckling or three port vitrectomy with or without lensectomy and sometimes both. In case of active developing disease with plus disease in stage IV or V, in some cases 3-5 days before the surgery bevacizumab 0.625 mg was injected.

Patients treated with laser were followed three days after the treatment and those with a surgery were followed the next day. The rate of improvement were inspected in the next week and then followed up to the third week. According to their responses, they were monitored from weekly to once in 6 months. It is important to note that the patients were followed at least 6 months after the treatment and the structural consequences were studied. The response to treatment in laser treated patients was defined as regression of plus and new vessels if existed and in patients with buckling or vitrectomy procedure was defined as retinal reattachment. Anatomical success for stage 4A was defined as complete retinal attachment. For stage 4B, partial

residual retinal detachment and for stage 5 at least posterior pole attachment. Unfavorable outcomes were described as media haziness, retrolental fibroplasias, macula dragging and retinal detachment. The effect of systemic factors on treatment was also assessed.

Ethical considerations

The possible outcomes were explained to the parents and consents were obtained. Timely treatments were performed for all the patients.

Results

Eight hundred-fifty nine neonates were screened during the 17 months who weighed less than 2,500 grams, of which 456 (53.1%) were males and 402 (46.9%) were females. The mean gestational age was 31.5 ± 3.2 weeks and the median was 32 weeks.

Average birth weight was $1,657.5 \pm 565.2$ g and the median was 1600 g. ROP was found in 734 eyes of the screened patients (40.3%). Highest prevalence of retinopathy in premature infants was in the weight range of 1,000-1,999 g (44%). Univariete analysis showed a significant relation between gestational age ($P=0.000$), age of first examination ($P=0.025$), age of referral ($P=0.000$), weight ($P=0.000$), duration of oxygen therapy ($P=0.000$) and ventilation ($P=0.000$), respiratory distress syndrome (RDS) ($P=0.000$), sepsis ($P=0.012$), intraventricular hemorrhage (IVH) ($P=0.006$) and ROP (Table 1). In a logistic regression analysis, after adjustment for weight, gestational age, RDS, duration of oxygen therapy, and age at admission, IVH, sepsis, duration of ventilation, age of examination, the gestational age ($P=0.000$, $OR=0.42$), weight ($P=0.000$, $OR=0.63$), RDS ($P=0.01$, $OR=0.64$), were significantly and inversely associated with ROP. The duration of oxygen therapy ($P=0.003$, $OR=1.25$) was significantly associated with ROP. Of the 734 eyes with ROP, 327 (44%) needed treatment. the prevalence of ROP was 42.8% with the highest frequency in stage 1 ($n=230$, 31.4%), stage 2 ($n=178$, 24.2%), stage 3 ($n=213$, 29%), stage 4A ($n=42$, 5.7%), stage 4B ($n=17$, 2.3%), stage 5 ($n=54$, 7.3%). Needing treatment were significantly and inversely associated with gestational age ($P=0.000$), age at the first referral ($P=0.000$), age at the first examination ($P=0.000$), birth weight

($P=0.000$) and RDS ($P=0.02$), and it was significantly and directly associated with the duration of oxygen therapy ($P=0.01$).

Of the 327 eyes with ROP also needed treatment 91 eyes were in stage 2, 147 eyes in stage 3, 38 eyes were in stage 4A, 16 were in stage 4B, 35 eyes in stage 5 (Figure 1A). Of all eyes that needed treatment 241 eyes (73.7%) were treated with laser in different stages and 202 (84%) regressed (Figure 1B) favorable outcome after laser treatment in prethreshold stage was (94%).

Regression after treatment were significantly and adversely associated with risk factors such as gestational age ($P=0.003$, $OR=0.53$), age at the first examination ($P=0.000$, $OR=0.69$), birth weight ($P=0.000$, $OR=0.58$), RDS ($P=0.001$, $OR=0.55$) (Table 2). In a logistic regression analysis attachment after treatment were significantly associated with gestational age at first examination ($P=0.021$, $OR=2.013$).

7.3% of the cases had unfavorable outcome after laser treatment. Unfavorable outcome was more in stage 5, stage 4B, stage 4A respectively. Among patients treated by laser 77% regressed in zone I ROP and 98% in zone II ROP.

Out of 231 patients who were treated by laser, 26 eyes (10%) needed additional therapy, the need for retreatment was decided according to the range of plus or new vessel after 3 weeks.

In this study, Avastin was used for 9 eyes as initial and, out of which 55% regressed. Four eyes, which were treated by laser and Avastin, did not regress and one eye had complete retinal detachment.

Twenty-eight eyes had vitrectomy at various stages, among them 21% had full retinal attachment, 17% partial attachment. For 23 eyes scleral buckling were performed. Out of which 4 eyes (17%), had full retinal attachment, 7 eyes (30%) had partial attachment. Out of 178 eyes which were in stage 2 laser treatment was done for 90 eyes with 89% (80 eyes) regression. Out of 213 eyes which were in stage 3 laser treatment was done for 132 eyes with 81% (108 eyes) regression, 4 eyes were treated with Avastin with 75% regression. Out of 42 eyes which were in stage 4A laser treatment was done for 19 eyes (45%) and 15 eyes (78%) regressed. One eye was treated by Avastin, which was

not regressed. Two eyes were treated by laser and Avastin, which none regressed. Out of three eyes, which were treated by vitrectomy none had retinal attachment, one eye had partial attachment. Of four eyes in stage 4A, which were treated with laser and scleral

buckling insertion, two eyes (50%) had full retinal attachment, of four eyes treated by scleral buckling one eye (50%) had full retinal attachment and one eye had partial attachment (Figure 2).

Table 1. Risk factors in retinopathy of prematurity

	ROP (Yes)	ROP (No)	P
Weight	1399.7890 (465.96669)	1801.3347 (556.66460)	<0.000
AGE of first exam			
AGE of first exam <26 wks	172	292	0.025
AGE of first exam 26-28 wks	63	76	"
AGE of first exam 29-30 wks	31	23	"
" 31-32 wks	14	14	"
" 33-34 wks	63	84	"
AGE at examination time (referral)			
<30 days	24	41	<0.000
30-59 days	265	377	<0.000
GA			
GA<26 wks	185	98	0.000
26-28 wks	151	349	0.000
Oxygen duration days	24.7647 (20.62253)	12.6200 (14.14993)	<0.000
Ventilation Duration days	11.7745 (18.37099)	4.4788 (10.56554)	<0.000
Sex M/F	188/158	265/240	0.67
Transfusion	131 (43.4%)	127 (25.9%)	<0.000
No	436 (89.9%)	91 (98.9%)	
Ventilation			
<7 days	214 (69.9%)	429 (86.7%)	
7-13 days	23 (7.5%)	37 (7.5%)	
14-21 days	27 (8.8%)	14 (2.8%)	<0.000
>21 days	42 (13.7%)	15 (3.0%)	
Oxygen			
<7 days	72 (23.5%)	237 (47.9%)	
7-13 days	35 (11.4%)	87 (17.6%)	
14-21 days	44 (14.4%)	82 (16.6%)	<0.000
>21 days	155 (50.7%)	89 (18.0%)	
RDS			
Yes	209(68.8%)	257 (52.0%)	<0.000
No	95 (31.3%)	237 (48.0%)	
Sepsis			
Yes	25 (8.2%)	21 (4.3%)	0.01
No	281 (91.8%)	473 (95.7%)	
Phototherapy			
Yes	229	385	0.21
No	76	110	
IVH			
Yes	27	21	0.006
No	274	475	

ROP: Retinopathy of prematurity
GA: Gestational age
RDS: Respiratory distress syndrome
IVH: Intraventricular hemorrhage

Table 2. Analysis of risk factors for ROP regression after laser therapy

Risk factor	Regressed ROP	Non regressed	P	Odd ratio
Gestational age				
26>week	157	130	0.000	0.53
26-28 week	178	335		
Age first examination				
Age<29 days	208	264	0.025	0.69
Age 30-56 days	70	274		
weight				
500-900 g	35	33	0.000	0.58
1000-1499 g	158	132		
1500-1999 g	102	193		
>2000 g	45	155		
Ventilation duration				
>7 days	235	407	0.000	1.039
7-13 days	27	26		
14-21 days	24	29		
>21days	51	47		
Oxygen duration				
>7 days	102	225	0.000	1.022
7-13 days	47	82		
14-21 days	64	68		
>21 days	125	133		
RDS	227	271	0.001	0.55

RDS: Respiratory distress syndrome

Out of 17 eyes in stage 4B, out of 6 eyes treated by vitrectomy four eyes (75%) had partial attachment, one eye (25%) had full attachment. Of 6 eyes treated by scleral buckling 3 eyes (75%) had partial attachment, one eye (25%) had total attachment, and two eyes were not operated due to refusal of the parents and one eye was inoperable (Figure 3).

Of 54 eyes which were in stage V, 15 eyes (27%) had vitrectomy, which two eyes (13%) had full retinal attachment. Six eyes (11.1%) had scleral buckling, out of which one eye had full retinal attachment and two eyes had

partial retinal attachment. One eye had both scleral buckling and vitrectomy but there was no retinal attachment. Two eyes after vitrectomy treated by Avastin and one eye had three sessions vitrectomy but no retinal attachment was obtained and 10 eyes were inoperable (Figure 4).

Results were recorded and analyzed using descriptive statistics, χ^2 , univariate and multiple regressions. Correlation between outcomes and systemic factors in complete medical records was assessed.

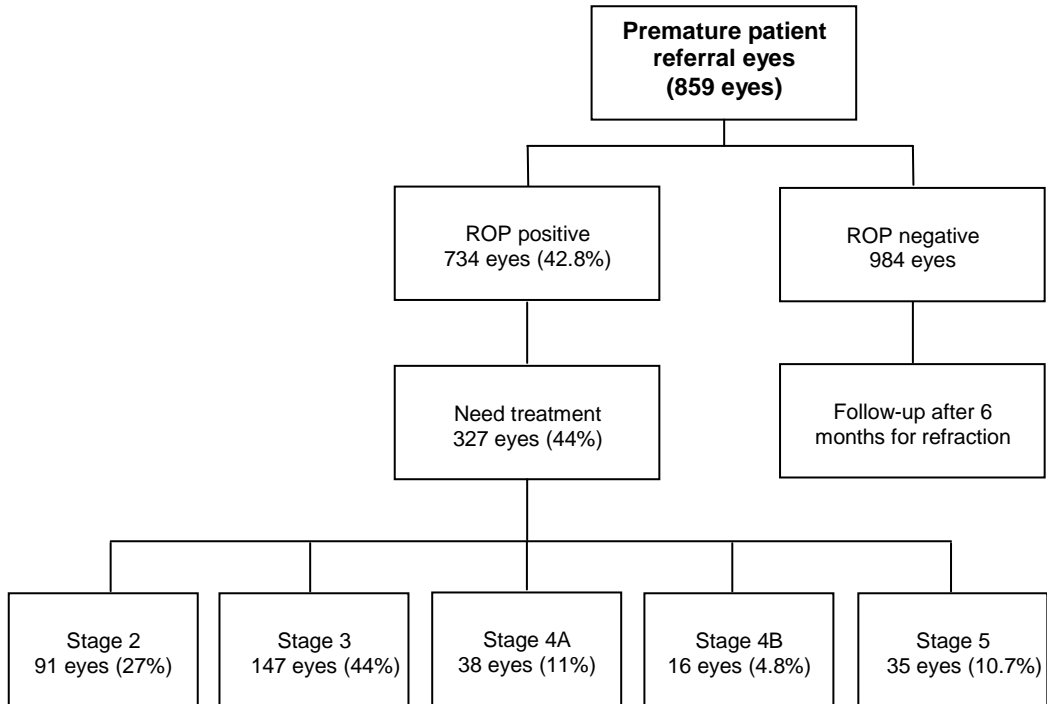


Figure 1A. Needing treatment according to the staging of Retinopathy of prematurity

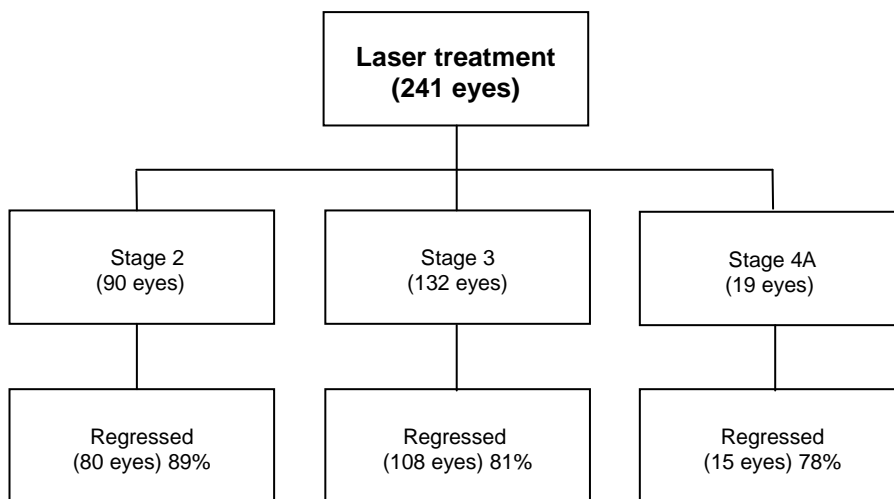


Figure 1B. Favorable outcome after Laser treatment

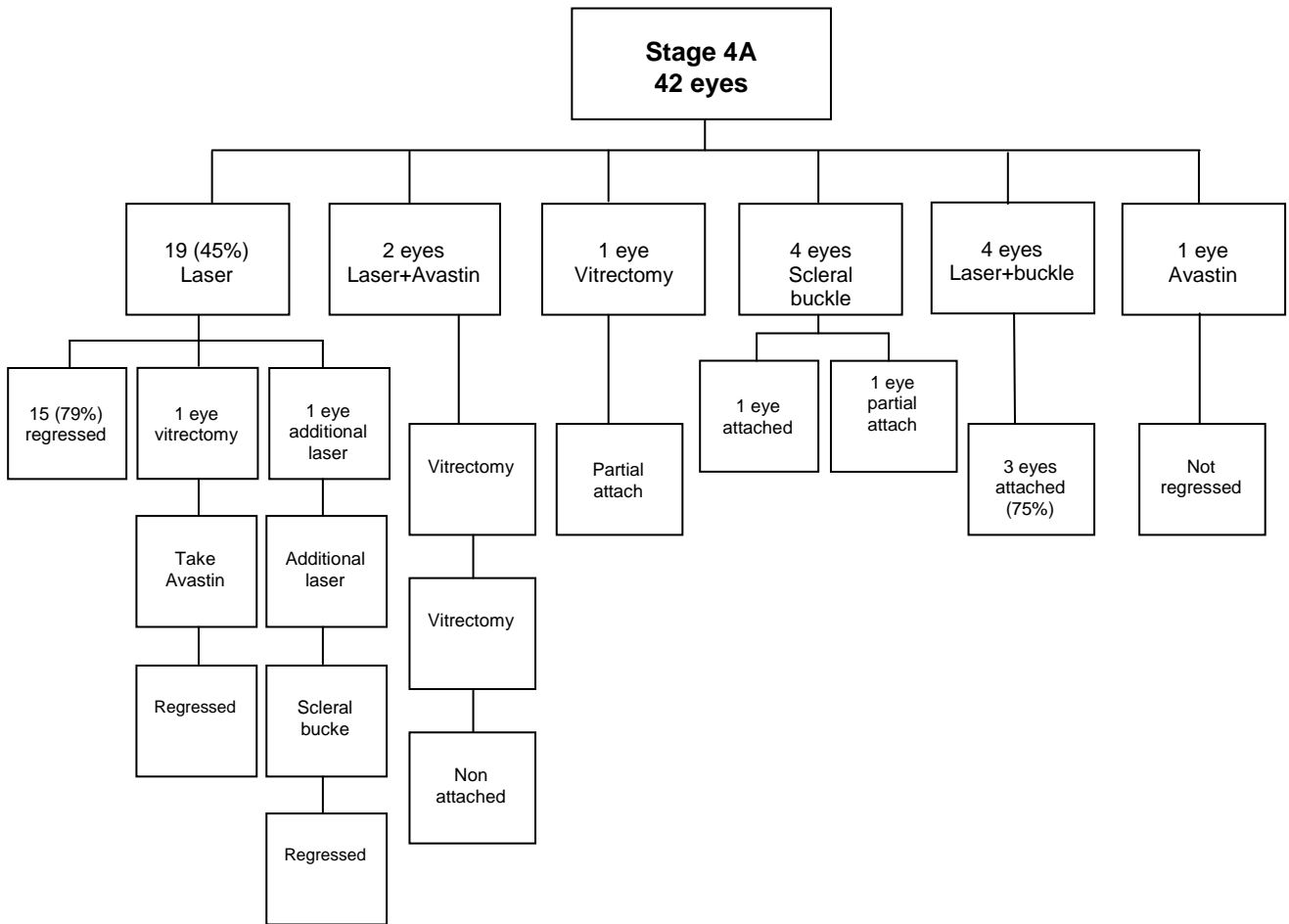


Figure 2. Intrevention for stage 4A and outcome

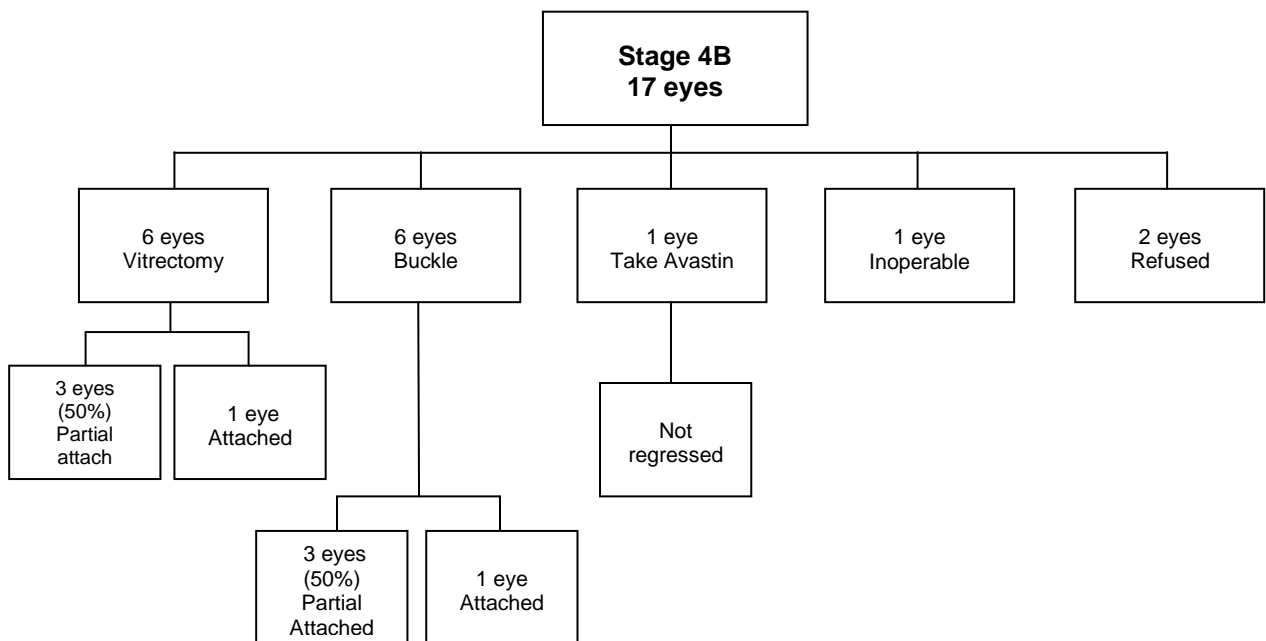


Figure 3. Intrevention for stage 4B and outcome

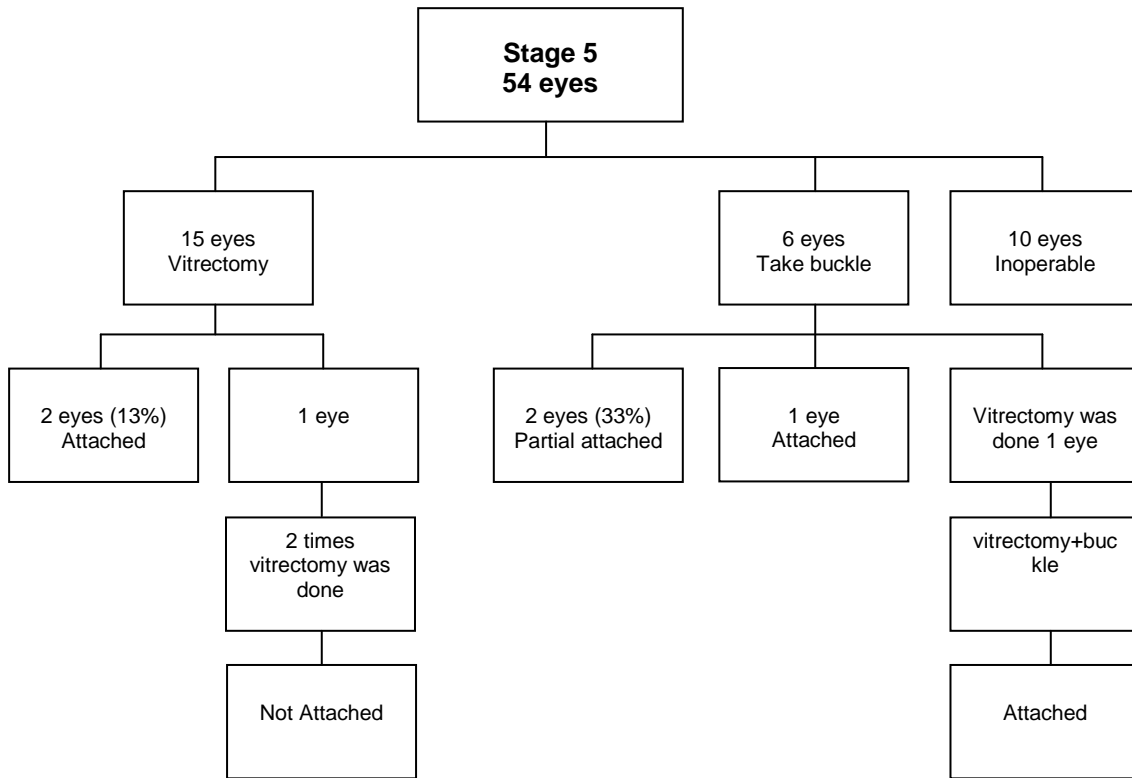


Figure 4. Intrevention for stage 5 and outcome

Discussion

This study investigates the structural outcome of ROP treatment on the neonates who needed treatment. This study showed that among 858 referred neonates weighing less than to or equal to 2,500 g to the Farabi Eye Hospital, the prevalence of ROP was 41.2% with the highest frequency in stage 1 and lowest in stage 4B. Other studies in developing countries, like India or Brazil, show lower prevalence of ROP in neonates.^{20,21} This may be due to higher under reported cases in these countries or better care for premature neonates.

In our study the highest prevalence of ROP was in stage 1 and in weight range of 1,000-1,999 g (44%), while the study of Grazyano et al, the prevalence of ROP in all stages was 29.9% and the most frequent cases of ROP was in neonates weighing less than 1,000 g (78.5%). This difference may be due to higher survive chances of infants weighing less than 1,000 g in Portugal.²²

In this study, favorable structural outcome following laser and vitrectomy was more

frequent with Huchenson et al report, frequency of posterior chamber hemorrhage was 36%.²³ In the study done by kychenthal et al favorable outcome was less than that of this study (64.4%).²⁴

In our study favorable outcome after laser treatment in prethreshold stage was (94%), which is less than other studies in developed countries.^{25,26} In a study done by Fleming et al in America, there was 100% favorable structural outcome following the laser treatment for prethreshold stage.²⁵ In this study overall side effects was 14%, in the study done by Vander prevalence of side effects in zone 1 of prethreshold stage were 16%, while in the threshold stage the prevalence was 18%.²⁶

In this report, patients who were treated with laser in the threshold level had 82% of favorable outcome. Other studies showed different level of favorable outcome of laser therapy in the threshold stage. In a study done by Capone, Georgiana the prevalence of undesirable outcome in patients who had

been treated with laser in stage threshold was lower than this study.²⁷ While in a study done by Shapiro et al the unfavorable outcome following laser therapy in zone I was more than that of our study.²¹

In a study done by Katz et al, which studied the unfavorable outcome of laser therapy in different phases of disease development, showed that in the zone I the unfavorable effects were 40% while in the zone II, it was 9.8% which is contradictory to the results of this study.²⁸

In the investigation done by Foroozan et al the favorable outcome of laser treatment was more than our study (91%) but also retinal detachment was higher as compared to this study (9%) and retrolental fibroplasia was similar to this study.²⁹

In this study unfavorable outcome of laser treatment in zone I was 10% while in report of Okeefe et al, it was 78% even after the insertion of the scleral buckle in 10 eyes the desired outcome was not observed and the desired outcome of treatment done in the prethreshold level was very low.^{29,30}

In this study patients with ROP (zone 1 stage III with or without plus) had 64% of favorable structural outcome.

In a report on early treatment of ROP (zone I 1, level 3 with or without plus) the unfavorable structural outcomes are indicated to be 30.8% which is less than this study.⁷

In this study, patients in stage 4, had 13% partial retinal attachment following buckle and

6.7% following vitrectomy and 1% had complete retinal attachment after being treated with the scleral buckle, while in a study done by Hartnet et al, there was a major difference in outcome of the treatment with the scleral buckle.³¹

In this report 15% of all the patients treated with the surgery had favorable outcome, and in stage V, full retinal attachment and partial retinal attachment were observed less than the study conducted by Roohipoor et al on patients who had vitrectomy at stage V,³² and also in another study conducted by Kychenthal.³³

Conclusion

Laser therapy in ROP resulted in better structural outcome in the prethreshold status compared to the threshold status. Favorable outcome of vitrectomy was more than that of the scleral buckling. Unfavorable outcome was more frequent in stage 5, stage 4B, stage 4A, respectively. Predictive factor for regression after laser was gestational age, birth weight, RDS, duration of oxygen therapy, and for postsurgical attachment was age of first examination.

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