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Original Article

Retinopathy Screening of Premature Neonates Born at Gestational Age 32-36 Weeks

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ABSTRACT

Background: Retinopathy of prematurity (ROP) may cause decreased visual acuity and even blindness. This study aimed to extend ROP screening to late-premature neonates.

Methods: The study evaluated the results of ROP screening in premature neonates with gestational age (GA) of 32-36 weeks and six days in Tehran, Iran, using the medical records of neonates admitted to NICU from 2007 to 2018. These neonates had respiratory distress and received supplemental oxygen. They underwent a complete retinal examination on the 28th day of birth. The neonates with complications such as syndromic disorders, congenital heart disease, metabolic disorders, or surgical needs were excluded from the study.

Results: The study included 415 premature neonates (equal ratio of each gender) with a mean GA of 33.4 weeks and a mean birth weight (BW) of 1886 grams, of whom 76 (18%) had ROP and 11 (2.7%) needed ROP treatment.
Neonates with ROP had lower GA and BW compared to neonates without ROP (32.7 versus 33.5 weeks, P=0.000039, and 1698 versus 1929 grams, P=0.05, respectively).
Detailed patient records available for 163 neonates showed that compared to neonates without ROP, the ROP group had increased mean time for oxygen therapy (118±115 versus 44±49 hours, P<0.001) and hospitalization duration (24±20 versus 10±8 days, P<0.001).

Conclusion: Neonates with GA of up to 35 weeks who had an unstable clinical course or any high-risk factor for developing ROP may need to be screened for the presence of ROP to prevent adverse outcomes. The obtained results showed that lower GA, lower BW, increased oxygen-therapy duration, and longer hospitalization duration are risk factors for developing ROP.

Keywords: Blindness, Neonate, Oxygen therapy, Retinopathy of prematurity, Visual impairment

Introduction

The retina is a light-sensitive tissue that lines the back of the eye. Retinopathy of prematurity (ROP) is a retrolental fibroplasia due to the growth of fibrous tissue behind the lens. ROP is defined as incomplete vascularization of the retina in premature newborns and can lead to neovascularization and its sequelae (1). The abnormal blood vessels are fragile and may leak, leading to potential retina scarring. When severe, this scarring may cause retinal detachment, which is the main cause of visual impairment and blindness in ROP (1,2).

The rate of blindness due to ROP is less than 10% in developed countries, while it has been found to be close to 40% in developing countries (3). Prematurity and low birth weight (BW) are the most prevalent causes of ROP. Still, other factors may also play a role such as concentration and duration of oxygen therapy, duration of mechanical ventilation treatment, neonatal sepsis, blood transfusion, intraventricular hemorrhage, serum bilirubin level, duration of phototherapy, acute neonatal respiratory distress syndrome, lack of surfactant administration, ambient light,

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anemia, the high blood concentration of carbon dioxide, and low concentration of oxygen (4-6).

Studies showed signs of ROP in 66% of newborns with BW≤1250 grams and 82% of newborns with BW<1000 grams (7). Moreover, in newborns weighing 1250 grams or less, there is an increased risk of ROP progression that warrants treatment, also known as threshold ROP (7).

Current ROP screening guidelines are largely based on studies conducted in high-income countries. However, there is evidence that neonates in low- and middle-income countries may have vision-threatening ROP at higher BW and GA (8,9). Another study found that if the screening criteria recommended in the United States are to be used in Iran, 8.4% of Iranian infants with ROP who need treatment would not be identified and diagnosed (10).

Due to the differences in the ROP screening guidelines appropriate for premature neonates between developed countries and Iran, this study aimed to examine the prevalence of ROP and factors associated with retinopathy in hospitalized premature neonates with GA <37 weeks (up to 36 weeks and six days) , thus extending ROP screening to an older age than the age recommended by screening guidelines for developed countries. This will help determine the cut-off gestational age for ROP screening. The earlier diagnosis and treatment of this disease in at-risk newborns reduces the likelihood of preventable childhood blindness and its related complications.

Methods

This retrospective study with a final sample size of 415 (after considering the exclusion criteria) was a multicenter collaboration between the neonatal intensive care units (NICUs) and maternity wards in multiple hospitals of Shahid-Beheshti University of Medical Sciences (SBMU) in Tehran, Iran. This study included all premature neonates with GA <37 weeks (up to 36 weeks and six days) who were admitted to the NICU due to respiratory distress and general illness and were considered to have an unstable clinical course. Investigation of patients' records from March 2007 to March 2018 led to the identification of 415 neonates with the above criteria who entered the study for the primary statistical analyses. However, detailed statistical analyses were performed on data obtained from163 neonates whose medical records of hospitalization and oxygen therapy duration were available. Neonates with underlying medical disorders, such as syndromic disorders, known congenital heart problems, metabolic disorders, or surgical problems, were excluded from the study. All neonates undergoing oxygen therapy and/or mechanical ventilation at some point during their hospitalization were included in the study. Patients who did not attend the follow-up ophthalmologist visit were excluded from the study. All neonates at 28 days of age underwent complete retinal examination by an ophthalmologist with expertise in ROP using an indirect ophthalmoscope after dilation of the pupil with a solution containing tropicamide (0.5%) and phenylephrine (2.5%) drops. Data were collected from hospital records of neonates and their mothers.

This study followed the Helsinki Declaration in terms of patients' rights and confidentiality. The study protocol was approved by the Research Ethics Committee of SBMU (IR.SBMU.MSP.REC. 1400.065). Informed consent was waived due to the retrospective nature of the study. Since the study was performed retrospectively using the patients' records, no additional costs were imposed on patients for their ROP screening.

In this study, the data were presented as mean, standard deviation, frequency, and percentage. Chi-square or Fisher's exact tests were used to compare qualitative variables between the two groups of neonates with and without ROP. In addition, the t-test was used to compare the quantitative variables. All statistical analyses were performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA). P-values ≤0.05 were considered statistically significant.

Results

The study sample included 415 neonates with a mean GA of 33.36 ±1.2 weeks and mean BW of 1886±446 grams and an equal ratio of males and females. In total, 76 (18%) neonates had some form of ROP, including 12 (2.9 %) unilateral and 64 (15.4%) bilateral ROPs. Out of neonates with ROP, 11 (2.7%) needed ROP treatment and one (0.24%) needed additional non-ROP surgical eye treatment. Additionally, there were 76 neonates with GA of 35 weeks and above, and one neonate had a BW of 1580 grams and needed ROP treatment. However, in long-term follow-up (not included in the tables), 88 (21%) neonates needed medical and surgical management of non-ROP eye diseases, and a total of 100 (24 %) neonates needed some type of ophthalmologic care.

Neonates with ROP had lower GA and BW compared to neonates without ROP (32.7 versus 33.5 weeks, P=0.000039, and 1698 versus 1929

grams, P=0.05, respectively).

In the ROP group, neonates needing ROP treatment had a mean±SD GA of 32.4 ±0.9 weeks and a mean±SD BW of 1433 ±359 grams, while the ROP group who did not need treatment had a mean±SD GA of 33.4 ±1.2 weeks (P=0.107) and a mean±SD BW of 1899±442 grams (P=0.005). These results showed that in neonates with ROP, lower BW increased the likelihood of the need for ROP treatment.

Among neonates with ROP, two (0.48%) had unilateral stage 4. The first case (with GA of 32 weeks and BW of 1330 grams) received laser treatment with additional laser therapy in areas that failed to respond initially and regressed with the acceptable anatomic outcome afterward. The second neonate (with GA of 35 weeks and BW of 1580 grams) received band O.D. (band oculus dexter, i.e., right eye) and anti-vascular endothelial growth factor therapy injection OU (oculus uterque, i.e., both eyes) which was accompanied by dragging of vessels and encroachment of foveal avascular zone. Moreover, one (0.24%) of the neonates without ROP underwent vitrectomy O.D. due to vitreous hemorrhage.

As mentioned previously, non-ROP eye findings were detected in the long-term follow-up of 88 (21%) neonates, and some of these findings were important based on the visual outcomes. These included vitreous hemorrhage, anisometropia, high hyperopia (more than 6 diopters before 40 weeks post-conception), anterior segment dysgenesis, anterior segment and lid finding in ichthyosis, cryptophthalmos, delayed visual maturation, cataract, corneal opacity, micro cornea, strabismus, optic atrophy, congenital toxoplasmosis and TORCH syndrome [(T)oxoplasmosis, (O)ther Agents, (R)ubella, (C)ytomegalovirus, and (H)erpes Simplex], myopia, high cylinder, anophthalmia, blepharoptosis, chorioretinal coloboma, adenoviral conjunctivitis, and nasolacrimal duct obstruction.

In the group of neonates with GA of 34 weeks, there was no case of ROP with the need for treatment. One neonate in the group of neonates with GA of 36 weeks underwent a deep vitrectomy due to a vitreous hemorrhage, and it was noted that the delivery had been traumatic and complicated. Tables 1 and 2 present the results of 415 neonates and Tables 3-5 present the detailed statistical analysis of data from 163 neonates whose records of hospitalization and oxygen therapy were available. Data showed increased mean±SD time for oxygen therapy (118±115 hours versus 44±49, P<0.001) and increased mean±SD for hospitalization duration (24±20 days versus 10±8, P<0.001) in the group of neonates with ROP, compared to those without ROP. There was no difference between the two study groups in terms of the birth sequence and number of children born to the mother. It was also found that BW<1500 grams increased the likelihood of developing ROP (P<0.001).

Among mothers of neonates without ROP, 11 (8.6%), 17 (13.3%), and 19 (9.4%) had high blood pressure, diabetes, and thyroid dysfunction, respectively. However, among mothers of neonates with ROP, 1 (2.9%), 8 (22.9%), and 1 (2.9%) had high blood pressure, diabetes, and thyroid dysfunction, respectively. There was no statistically significant difference in the prevalence of maternal health conditions between the two groups.

Table 1. Distribution of neonates based on gestational age and mean birth weight

Gestational Age (week)	Screened Neonates N=415	Mean Birth Weight (gram)	ROP N=76	Needed Ophthalmic Management N=22	Needed ROP Treatment N=11	Needed Non-ROP Eye Care N=11	ROP Stage 4 and 5
32	134	1679	45	11	9	2	1
33	99	1860	19	4	1	3	0
34	106	2027	7	3	0	3	0
35	47	2084	4	3	1	2	1
36	29	2111	1	1	0	1	0

Odds ratio calculation showed that the gestational age of 32 weeks increased the likelihood of retinopathy of prematurity occurrence by 2.4 times compared to the gestational age of 33 weeks (95% CI: 1.3008- 4.4086, P=0.0050).

Table 2. Comparison of the number and frequency of neonates with birth weight less than 1500 grams among neonates with and without retinopathy (n=415)

		No ROP (n=339)	ROP (n=76)	P-value
Birth Weight (gram)	≤1500	58 (72%)	23 (28%)	0.010*
	>1500	281 (84%)	53 (16%)	

* P-values less than 0.05 indicate statistical significance.
P-value was calculated based on the odds ratio test (OR=2.1025, 95% CI: 1.1948-3.6998).
Neonates with birth weight less than 1500 grams were 2.1 times more likely to have ROP.

Table 3. Neonatal characteristics for neonates with and without retinopathy of prematurity (n=163)

Neonates		Total	No ROP (n=128)	ROP (n=35)	P-value
Delivery Method	Vaginal	23 (14.1%)	21 (16.4%)	2 (5.7%)	0.107
	C-Section	140 (85.9%)	107 (83.6%)	33 (94.3%)	
Living Child	1.00	71 (48.3%)	53 (47.3%)	18 (51.4%)	0.93
	2.00	57 (38.8%)	45 (40.2%)	12 (34.3%)	
	3.00	15 (10.2%)	11 (9.8%)	4 (11.4%)	
	4.00	1 (0.7%)	1 (0.9%)	0 (0.0%)	
	5.00	3 (2.0%)	2 (1.8%)	1 (2.9%)	
Hospitalization Duration (day)		12.61±12.9	9.6 ±7.9	23.6±20	<0.001*

*P-values less than 0.05 indicate statistical significance.
Among mothers of 163 neonates included in the study, 23 mothers (14%) had a normal vaginal delivery and 140 (86%) had cesarean section delivery. There was no significant difference in the type of delivery between neonates with and without ROP.

Table 4. Comparison of some indexes in neonates with and without retinopathy (n=163)

	No ROP (n=128)	ROP (n=35)	P-value
Intubation Duration (hour)	42.41 ±35.74	66.35 ±67.12	0.105
Oxygen Therapy (hour)	44.35 ±49.24	118.07 ±114.54	<0.001*

*P-values less than 0.05 indicate statistical significance.
The ROP group had longer oxygen-therapy duration.

Among neonates with ROP, 2 (5.7%) and 3 (8.6%) had intrauterine growth restriction (IUGR) and persistent pulmonary hypertension in the neonate (PPHN), respectively. However, among neonates without ROP, two (1.6%) and one had PPHN and aspiration, respectively. Neonates with ROP had a statistically greater likelihood of having medical conditions other than ROP (P=0.006).

In the group of neonates with ROP, five (14.3%) had germinal matrix hemorrhage (GMH) grades I or II detected on ultrasound compared to only four (3.1%) neonates in the group of neonates without ROP, indicating that neonates with ROP had an increased likelihood of having GMH (P=0.01).

Table 5. Clinical records of mothers and their neonates with and without retinopathy (n=163)

		No ROP (n=128)	ROP (n=35)	P-value
Maternal Disease	None	88 (68.8%)	25 (71.4%)	0.105
	HTN	11 (8.6%)	1 (2.9%)	
	DM	17 (13.3%)	8 (22.9%)	
	Hypothyroidism	12 (9.4%)	1 (2.9%)	
Neonatal Disease	No disease	125 (97.7%)	30 (85%)	0.006*
	IUGR	0 (0.0%)	2 (5.7%)	
	PPHN	2 (1.6%)	3 (8.6%)	
	Aspiration	1 (0.8%)	0 (0.0%)	
Neonatal Sonography	None	124 (96.9%)	30 (85.7%)	0.01*
	GMH I,II	4 (3.1%)	5 (14.3%)	
	GMH III.IV	0 (0.0%)	0 (0.0%)	
Stage	1.00	1 (100.0%)	7 (30.4%)	0.555
	2.00	0 (0.0%)	5 (21.7%)	
	3.00	0 (0.0%)	8 (34.8%)	
	4.00	0 (0.0%)	3 (13.0%)	
Blood Transfusion	Yes	2 (1.6%)	2 (5.7%)	0.159
Sepsis	Yes	2 (1.6%)	1 (2.9%)	0.614

*P-values less than 0.05 indicate statistical significance. Chi-square calculated the p-values.
ROP: Retinopathy of Prematurity
DM: Diabetes Mellitus
GMH: Germinal Matrix Hemorrhage
PPHN: Persistent Pulmonary Hypertension in the Neonate
IUGR: Intrauterine Growth Restriction
HTN: Hypertension

Discussion

The present study showed that the prevalence of ROP among our patient population was 18%. It also found that extending ROP screening to 35 weeks of GA among premature neonates with an unstable clinical course might prevent missed ROP diagnosis. ROP is among the most important causes of preventable blindness in children in both developed and developing countries. In the United States, ROP is the second leading cause of

blindness in children after cortical impairment. ROP can have lifelong side effects; therefore, even infants with mild retinopathy who recover without any evident signs of damage are more likely to develop myopia, amblyopia, astigmatism, strabismus, or cataracts, later in life. These patients need to be followed up for a lifetime (1,11).

The gold standard for ROP diagnosis is indirect ophthalmoscopy (1). For ROP screening, the indirect ophthalmoscopy was performed by an ophthalmologist who was an expert certified in ROP screening. Based on the obtained data, most of the ROP patients (9/11 or 82%) who needed treatment were in the group of neonates with GA of 32 weeks. Therefore, this GA group needs to be screened to avoid missing any case of ROP. A neonate with a BW of 890 grams needed ROP treatment in the group of neonates with a GA of 33 weeks. This finding along with intrauterine growth restriction constitutes a risk factor for developing ROP (4). In total, there were 76 neonates with GA ≥ 35 weeks, of whom one neonate had ROP and needed treatment. This is an important finding based on the objective of our study and explains why it is important to extend the ROP screening to GA of 35 weeks. Low BW may have been a risk factor for developing ROP.

Our results showed that the mean BW and mean GA of neonates with ROP were significantly lower than those without ROP. This suggests that lower weight or GA of a preterm neonate at birth increases the risk of developing ROP. The results of a study performed by Naderian et al., in 2009, revealed that the prevalence of ROP in infants weighing less than 1500 grams and infants weighing more than 1500 grams was 22.9% and 6.6%, respectively (12). In contrast, another study found that the prevalence of ROP in neonates with BW less than 1500 grams were approximately 60% (13). The findings of the present study demonstrated that 28% of neonates with BW<1500 grams had ROP, which was the same range described by prior studies.

A study conducted by Reynolds et al. in India, in 2002, showed that the screening criteria for ROP were BW ≤1750 grams or GA≤34 weeks (14). However, their study sample consisted of neonates with lower GA compared to our sample. In the United States, ROP screening is performed on neonates with a BW of ≤1500 grams or a GA of ≤30 weeks (15). In Asian countries, neonates often develop ROP at higher BWs and GAs, compared to those reported in the Western literature (16). Guidelines suggest that preterm neonates with BW ≤2000 grams and GA≤34 weeks should be screened for ROP. However, if the neonate is clinically ill or unstable, or there is any high-risk factor for developing ROP, larger babies with GAs of 34-36 weeks may need to be screened as well (17).

In a study performed by Mansouri et al. in 2007, the frequency of ROP among 147 neonates with very low birth weight (VLBW) or low GA was 29.9%. The mean±SD BW for their study sample was 1386 ±356 grams compared to 1886 ±446 grams in our study (18).

Previous studies have demonstrated a positive association between high-concentration oxygen therapy and the prevalence of ROP in premature newborns. Limiting the oxygen concentration to 40% in oxygen therapy of premature newborns was associated with reducing the rate of blindness caused by ROP. However, this oxygen reduction increased the mortality rate and the rate of cerebral palsy (19).

Consistent with our results, studies conducted by Karkhaneh et al. (2008) and Saeidi et al. (2017) on premature infants showed a negative association between GA and BW with the prevalence of ROP in preterm infants (20,21). The mean±SD GA and BW of infants with severe ROP in the study conducted by Karkhaneh et al. were 28.8±2.4 weeks and 1256±389 grams, respectively, while in our study, the mean GA and BW of ROP infants were 32.66 weeks and 1698 grams, respectively. Their study found that 329 (34.5%) out of 953 premature neonates had different grades of ROP. In both studies, the mean GA of neonates with ROP was significantly lower than neonates without ROP.

In our study, the mean±SD hours of oxygen therapy in neonates with ROP was significantly higher compared to the neonates without ROP (118±115 hours versus 44±49 hours). Many other studies referred to oxygen therapy as an important risk factor for developing ROP in premature infants, which confirmed our findings (4,22,23).

A study conducted in Iran showed that the appropriate ROP screening criteria for infants in Iran included GA≤32 weeks or BW ≤2000 grams (10), and that this criterion has a sensitivity of almost 100% in diagnosing infants with ROP requiring treatment, and can prevent the need for unnecessary ophthalmic examinations (10). However, our study results showed neonates with GAs and BWs greater than these thresholds requiring ROP screening.

Considering longer-term follow-up, our data

showed that a large number of our study population (n=100, 24 %) needed ophthalmologic care. This may show the importance of ophthalmologic care in this group. The presence of ROP alone does not always mean that the neonate needs treatment. However, it is very important to screen unstable hospitalized neonates to identify any ROP cases that might need treatment. ROP screening is a traumatic and invasive process; therefore, we must limit the number of visits and detect those who need treatment. For the likelihood ratios (LR), a publication has reported the following indicators for indirect ophthalmoscopy: for ROP-RT (requiring treatment), LR+ has been reported at 44.5 (95% CI: 11.3 -175.2), and LR- has been reported at 0.05 (0.00-0.77) (24). Neonates had follow-up visits with the retinopathy-expert researcher, which was in line with the test-retest method for measuring reliability.

Limitations

Larger sample size can increase the statistical power of the study. Limitations of the present study included incomplete patient records and loss to follow-up.

Conclusion

Our study reported that the prevalence of ROP among our patient population was 18% and that ROP screening may need to be extended to GA of up to 35 weeks with an unstable clinical course or any high-risk factor for developing ROP to prevent adverse outcomes.

Our data showed that lower gestational age, lower birth weight, increased duration of oxygen therapy, and longer duration of hospitalization are risk factors for the development of ROP among neonates with GA of fewer than 37 weeks (up to 36 weeks and six days).

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Conflicts of interest

None.

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