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Retinopathy of prematurity progression and its related factors: A cohort study in preterm infant in northern Iran

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ABSTRACT

Background and Objective: Retinopathy of Prematurity (ROP) is a vasoproliferative retinal disease in premature infants, causing lifetime visual impairment and blindness at an early age. The aim of this study was to investigate the impact of oxygen profile in the progression of ROP.

Methods: This prospective cohort study (from 2010 to 2020) was applied in the Ophthalmology center of Ayatollah Rouhani Hospital in Babol (Babol University of Medical Sciences, Babol, Iran) included 828 infants (<37 weeks of gestation with a birth weight <2500 g). Moreover, the oxygen profile of infants (with/without ROP) was collected from their history profile in terms of arterial blood gas.

Findings: The duration of oxygen therapy was significantly higher in ROP patients (9.19±14.33 days), compared to control (3.16±4.35 days), (P=0.002). The minimum level of PO_2 was significantly lower in ROP infants (51.71±44.81 mmHg) compared to controls (92.75±65.45 mmHg, P<0.001). Furthermore, patient with zone 1 involvement had higher PO_2 level than the patient with zone 2 involvement (P=0.029). The ventilation requirement was more frequent in ROP patients (39.27%) compared to controls (19.24%, P<0.001). Also, the CPAP requirement was more frequent in ROP patients (48.51%) compared to controls (32.95%, P<0.001).

Conclusion: Our results have indicated that the duration of oxygen therapy and the minimum and maximum level of PO_2 are indicators of ROP occurrence.

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Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disease in premature infants affecting the premature development of the respiratory system of premature infants [1, 2]. This infantile disease causes lifespan blindness or visual impairment at an early age [3, 4]. ROP is characterized by abnormal intravitreal neovascularization in the retina, which is a result of impairment in the development of the lungs [5, 6]. ROP severity has divided into five stages which start with the primary phase and anticipate advanced ROP that comes with hemorrhage, fibrovascular alterations, vitreoretinal traction, and retinal detachment [7, 8]. Moreover, three zones of the retina are involved in ROP, which indicates the rate of ROP involvement in terms of vascularization manner. Low birth weight, hypoxia, and low gestational age are the risk factor that has been proved in the pathogenesis of ROP [9- 13].

Hypoxia plays a critical role in the development and progression of ROP. The hypoxic condition in the retina leads to aberrant metabolism in affected cells [14- 16]. As a pathophysiologic response, the hypoxic cells secret vascular endothelial growth factor (VEGF) which leads to angiogenesis in a fibrovascular proliferation manner. This abnormal angiogenesis causes retinal detachment, which progresses ROP [17- 19]. Therefore, the investigation of the correlation of the oxygen profile and progression of ROP helps to realize more facts about the progressive and prognostic factors in ROP infants. Also, there is no study on the impact of different oxygen-related factors, including blood gases, oxygen delivery system, oxygen saturation, oxygen delivery methods and so on, in the progression of ROP. In this study, we investigated the relation of the oxygen profile via ROP infants in the progression of ROP.

Methods

Design study and participant

This prospective census-based cohort study (from 2010 to 2020) was applied in the NICU center of Ayatollah Rouhani Hospital in Babol (Babol University of Medical Sciences, Babol, Iran) included 828 preterm infants (<37 weeks of gestation with a birth weight <2500 g). All infants with gestational age>37 weeks and birth weight >2500 gr as well as without incomplete medical records were excluded from the current study.

Data collection

All ophthalmic examinations were performed via a vitreoretinal surgeon ophthalmologist. Initial examinations were performed in referring time; one hour after the administration of 2.5% phenylephrine and 0.5% tropicamide and funduscopic examinations implemented by using a binocular indirect ophthalmoscope, 28D lens, scleral depressor, and pediatric speculum. The infants were separated into two groups in terms of ROP; the infants with no signs of ROP were considered as the control group, and infants with different stages of ROP were considered as the case group. In ROP cases, the regular ophthalmic follow-up examinations were continued, and treatment protocol, including anti-vascular endothelial growth factor injection, was conducted according to the international classification of retinopathy of prematurity (ICROP) criteria [20]. The Zones of ROP were categorized as bellow: Zone I (The area defined by a circle centered on the optic nerve), Zone II (The area extending centrifugally from the edge of Zone I), and Zone III (The residual temporal crescent of the retina anterior to Zone II). In addition, ROP severity was divided into five stages started with the primary phase and anticipated advanced ROP that came with hemorrhage, fibrovascular alterations, vitreoretinal traction, and retinal detachment, as ICROP criteria.

Besides, the oxygen profile, including days of oxygen therapy, maximum level of FiO_2, minimum level of PO_2, maximum level of PCO_2, level of HCO_3, level of PO_2 and CO_2, oxygen saturation percentage, ventilation requirement, and continuous positive airway pressure (CPAP) requirement of infants (with/without ROP) were collected from their medical recordings in terms of arterial blood gas (ABG).

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Statistical analysis

Statistical analysis was performed using the SPSS 21.0. Quantitative variables were reported with mean ±Std. Univariate comparisons of risk factors between the groups were evaluated by Chi-square and independent T-test. The level of significance was taken to be P <0.05 for all statistical tests.

Results

Correlation of oxygen profile with ROP status

In this study, 303 infants (of 828; 36.59%) had ROP. Regarding with oxygen profile of infants with ROP, the duration of oxygen therapy was significantly higher in ROP patients (9.19±14.33 days) compared to control (3.16±4.35 days), (P =0.002). Furthermore, the minimum level of PO_2 was significantly higher in non-ROP infants (92.75±65.45 mmHg) compared to ROP infants (51.71±44.81 mmHg) (P <0.001). Also, the maximum level of PO_2 was significantly higher in non-ROP infants (110.98±59.50 mmHg) compared to ROP infants (83.91±64.60 mmHg) (P =0.018). The CPAP and ventilation requirements were significantly correlated with ROP (p <0.001). In ROP infants, 39.27% of patients needed ventilation, while just 19.24% of non-ROP infants were required to ventilation (P <0.001). Additionally, 48.51% of ROP infants were required to CPAP, while 32.95% of non-ROP infants were required to CPAP (P <0.001). There was no significant correlation between other oxygen profile indicators and ROP (table 1).

Correlation of oxygen profile of premature infants and stage of ROP

The results show that the maximum pressure of O_2 was significantly different in different stages of ROP (P=0.05), (table 2). Also, multiple comparisons via Tukey HSD analysis indicated that maximum PO_2 was significantly different between stage 1 and stage 3 of ROP (P <0.042), (table 3). Furthermore, no other indicators of oxygen profile were correlated with stages of ROP.

Considering the results, the maximum pressure of O_2 was significantly different in various zone involvement of ROP (P =0.027). Further, the maximum pressure of CO_2 was significantly different in various zone involvements of ROP (P =0.048). Interval comparison of zones demonstrated that a significant difference of O_2 maximum pressure was related to the difference of O_2 maximum pressure between zone 1 and zone 2 (P =0.029), (table 4). As well, an interval comparison of CO_2 maximum pressure illustrated no significant correlations between different zones. Moreover, no other indicators of oxygen profile were correlated with zones of ROP.

Table 1. Correlation of oxygen profile and therapeutic requirements with ROP status in first examination

Factors	Unit	Total	Status		Status
			Non-ROP	Non-ROP	
Days of Oxygen Therapy	Days	4.47±8.31	3.16±4.35	9.19±14.33	**0.002**
Max of FiO_2	mmHg	52.82±21.88	51.83±20.10	54.53±25.56	0.409
Min of PO_2	mmHg	87.62±65.43	92.75±65.45	51.71±44.81	**<0.001**
Max of PO_2	mmHg	105.63±63.15	110.98±59.50	83.91±64.60	**0.018**
Min of PCO_2	mmHg	40.04±31.80	38.05±14.19	48.40±63.41	0.295
Max of PCO_2	mmHg	45.23±16.54	43.62±18.39	55.00±13.07	**<0.001**
PCO_2	mmHg	40.62±11.46	41.14±11.80	39.52±9.68	0.219
HCO_3	mEq/L	21.80±10.74	21.72±8.47	21.08±6.09	0.483
PO_2	mmHg	57.43±43.60	59.68±41.30	57.06±36.78	0.645
Oxygen Saturation	%	75.60±17.58	76.38±18.10	75.04±14.51	0.651
Ventilation Requirement	No	608 (73.43%)	424 (80.76%)	184 (60.73%)	**<0.001**
	Yes	220 (26.57%)	101 (19.24%)	119 (39.27%)	
CPAP Requirement	No	508 (61.35%)	352 (67.05%)	156 (51.49%)	**<0.001**
	Yes	320 (38.65%)	173 (32.95%)	147 (48.51%)	

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Table 2. Correlation of oxygen profile indicators and ROP in term of stage and zone

Oxygen indicator	Stages								Zone							
	Stage 1		Stage 2		Stage 3		F	p-value	Zone 1		Zone 2		Zone 3		F	p-value
	Mean	SD	Mean	SD	Mean	SD			Mean	SD	Mean	SD	Mean	SD		
Days of Oxygen therapy	9.652	12.5140	6.083	8.0158	13.188	22.0793	1.207	0.306	7.947	7.9685	11.815	19.6450	6.625	8.9135	0.763	0.471
Max of FiO_2	54.42	25.061	49.21	24.933	61.87	26.638	1.278	0.284	64.50	26.453	50.83	27.234	51.04	20.485	2.197	0.118
Min of PO_2	47.16	52.561	62.11	46.307	39.22	16.521	0.936	0.400	42.77	18.276	43.64	33.879	79.55	74.206	2.842	0.069
Max of PO_2	65.28	57.931	78.56	53.348	128.78	84.169	3.221	**0.050**	115.54	73.964	57.76	40.806	99.50	78.981	3.937	**0.027**
Min of PCO_2	67.125	102.5631	37.313	8.4673	37.100	10.8878	1.079	0.350	38.214	10.9064	39.444	8.1256	85.222	137.2396	1.869	0.168
Max of PCO_2	50.867	10.8487	57.714	17.8516	58.600	5.1897	1.448	0.248	61.214	10.5698	52.625	11.8596	48.250	15.4712	3.324	**0.048**
PCO_2	40.140	8.4579	39.105	10.8000	39.400	10.5501	0.126	0.882	39.044	8.9990	40.138	10.4064	38.615	8.7832	0.256	0.775
HCO_3	20.965	6.0932	21.381	6.4796	20.879	5.9200	0.060	0.942	20.444	2.1885	20.638	4.2781	22.500	10.3305	0.895	0.412
PO_2	61.400	46.0742	51.860	23.0070	54.412	32.8844	0.524	0.594	49.267	21.3724	53.151	28.1671	72.667	58.2106	2.232	0.115
Oxygen saturation	69.24	18.168	77.90	12.515	78.50	9.415	2.193	0.123	76.82	13.768	76.00	13.939	70.13	18.735	0.582	0.563

Table 3. Multiple comparisons of maximum PO2 in different stages of ROP

Interval comparison of	Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Stage 1 and stage 2	-13.278	20.709	0.798	-63.59	37.03
Stage 1 and stage 3and4	-63.500*	25.363	**0.042**	-125.12	-1.88
Stage 2 and stage 3and4	-50.222	25.363	0.130	-111.84	11.40

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Table 4. Multiple comparisons of maximum PO_2 and maximum PCO_2 in different zone of ROP.

Indicator	Interval comparison of	Mean Difference (I-J)	Std. Error	P-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Max of PO_2	Zone 1 and zone 2	57.777*	21.705	**.029**	5.00	110.56
	Zone 1 and zone 3	16.038	25.870	.810	-46.87	78.94
	Zone 2 and zone 3	-41.738	23.631	.194	-99.20	15.72
Max of PCO_2	Zone 1 and zone 2	8.5893	4.4768	.148	-2.367	19.545
	Zone 1 and zone 3	12.9643	5.4217	.057	-.304	26.233
	Zone 2 and zone 3	4.3750	5.2970	.690	-8.588	17.338

Discussion

Our results suggested that the number of days of oxygen therapy was significantly higher in ROP patients compared to control. The insufficient level of oxygen led to retinopathy in premature infants. Therefore, the requirement for oxygen was more in ROP infants. Like the current study, Teoh et al. showed that the duration of oxygen therapy was significantly correlated with the progression of ROP [21]. In addition, Higgins represented that the duration of oxygen therapy was correlated with ROP [22].

Our results revealed that the minimum level of PO_2 was significantly higher in non-ROP infants compared to ROP infants. These findings confirmed the more requirements for oxygen in ROP patients who received more oxygen, and the minimum level of PO_2 was higher due to the more oxygen therapy. Besides, similar to our results, York et al., PO_2 was introduced as a risk factor of ROP [23]. Moreover, Higgins's study indicated oxygen saturation as a critical factor in ROP [22]. Therefore, PO_2 can be a potent prognostic factor to indicate ROP status in premature infants.

CPAP and ventilation devices are two important machines to deliver a desired concentration of oxygen to premature infants. Our results showed that CPAP and ventilation requirements were significantly correlated with ROP. In ROP infants, 39.27% of patients required ventilation, while just 19.24% of non-ROP infants required ventilation, indicating a more severe condition in the insufficiency of oxygen in ROP infants compared to non-ROP infants. Further, 48.51% of ROP infants were required to CPAP, while 32.95% of non-ROP infants were required to CPAP. Mohagheghi et al. stated that the ventilation and CPAP application could be a critical factor in the reduction of ROP [24], which is consistent with the results of the present study. Further, Mohagheghi et al. represented that volume guarantee ventilation led to a reduction of ROP rate in premature infants. The ongoing study suggested holding a clinical trial to select the desired duration for ventilation and CPAP application in ROP patients.

Finally, the results of the present study exhibited that the maximum level of PO_2 was higher in stage 3 and more of ROP. On the other hand, the higher stage of ROP was observed in immature infants with a worse condition, requiring more duration of oxygen therapy. Therefore, it is regular that the maximum level of PO_2 is higher in stage 3 and more of ROP due to the worse condition of premature infants. The non-synchronized medical records, involvement of one medical center, inaccessibility to other factors, i.e., the lifestyle of the mother, and so on were the limitations of this study.

In conclusion, the oxygen profile is critical in ROP progression. The insufficient concentration of oxygen leads to a worse condition in ROP progression. The findings of the current study revealed that a high concentration of oxygen therapy was found in ROP patients. For an investigation of the predictive role of oxygen profile on ROP status, we recommend holding a trial on follow-up of the ROP infants in the hospitalization period and screening the value of arterial blood gases.

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Conflict of interests

The authors declare that there is no conflict of interest.

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Ethical Code

Institutional Ethics Committee Approval was obtained from the local ethics committee: (IR.MUBABOL.HRI.REC.1399.373).

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