Journal of
Babol University of Medical Sciences
JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

Investigating the Effect of Venous Oxygen Saturation Level and Partial Pressure of Oxygen on Retinopathy of Prematurity Improvement

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Article Type

Research Paper

ABSTRACT

Background and Objective: Retinopathy of Prematurity (ROP), as a retinal vasoproliferative disease, is affected by the incomplete development of the respiratory system of premature babies. Since premature babies suffering from ROP have a lower level of partial pressure of oxygen (PO_2), the present study was conducted to investigate the effect of PO_2 and venous oxygen saturation in treatment response of ROP patients.

Methods: This retrospective cohort study (2010-2020) was conducted in the neonatal intensive care unit of Ayatollah Rouhani hospital in Babol among 502 premature babies (less than 34 weeks of pregnancy and with a birth weight of less than 2500 grams). ROP was diagnosed and determined by an ophthalmologist based on the ICROP index on the first day of birth. Data related to PO_2 and venous oxygen saturation were collected from patients' files. After receiving standard treatment for ROP, patients were examined and compared in two groups of "completely cured" and "other patients" (including partial recovery, no change, and disease progression) in terms of the effect of PO_2 and venous oxygen saturation on the decrease or increase in stage (I to IV) and zone (I, II, III).

Findings: Of the 502 babies examined, 193 had stage I, 232 had stage II, 76 had stage III, 1 had stage IV, and 55 had zone I, 245 had zone II, and 202 had zone III involvement. The mean level of PO_2 and oxygen saturation between the two groups of "completely cured" patients and "other patients" did not have a statistically significant difference. The mean level of PO_2 and oxygen saturation between the three groups of patients with partial recovery, patients with no change and patients with disease progression did not show a statistically significant difference. Furthermore, the levels of PO_2 and venous oxygen saturation were not related to the change of stage and zone in patients with ROP.

Conclusion: The results of the study showed that lack of oxygen is effective in causing ROP and oxygen therapy has an effective role in the treatment of ROP patients, but the amount of oxygen at the beginning of ROP diagnosis is not related to the treatment process of ROP.

Keywords: *Retinopathy of Prematurity, Venous Oxygen Saturation, Partial Pressure of Oxygen*.

Received:
Jul 23rd 2023
Revised:
Aug 29th 2023
Accepted:
Sep 10th 2023

Cite this article: Haghshenas Mojaveri M, Akbarian Rad Z, Rasoulinejad SA. Investigating the Effect of Venous Oxygen Saturation Level and Partial Pressure of Oxygen on Retinopathy of Prematurity Improvement. *Journal of Babol University of Medical Sciences*. 2023; 25(1): 427-33.

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[DOI: 10.22088/jbums.25.1.427]

Introduction

Retinopathy of Prematurity (ROP), as a retinal vasoproliferative disease, is affected by the incomplete development of the respiratory system of premature babies (1). ROP is characterized by abnormal neovascularization in the retina caused by impaired lung development. As a result, this disease is directly related to the level of oxygen in the blood of newborns (2). This disease can lead to lifelong blindness or visual impairment at a young age. In the fourth month of pregnancy, the fetal retina begins to vascularize. Blood vessel formation appears to be very sensitive to the amount of oxygen supplied naturally or artificially. In rare cases, mutations in the NDP gene have been found in some ROP patients, which are usually associated with Norrie disease (3).

Various risk factors, including prematurity, high oxygen exposure, low birth weight, various infections, heart defects, anemia, and low vitamin E levels are involved in the development of ROP (4). The main element of the disease in the pathophysiology of ROP is fibrovascular proliferation (5, 6). After abnormal angiogenesis, which is often progressive, fibrous tissue (scar tissue) is formed which may contract and cause retinal detachment (7).

The stage of ROP is divided into five stages, the advanced stages of which lead to hemorrhage, fibrovascular changes, retinal stretching and retinal detachment. In addition, ROP affects three zones of the retina, indicating the level of vascular involvement. Risk factors for ROP include low birth weight, hypoxia, and early maternal age (2, 8). Hypoxia plays an important role in the development and progression of ROP by causing abnormal metabolism in damaged cells. Hypoxic cells secrete vascular endothelial growth factor (VEGF), which leads to abnormal angiogenesis and retinal detachment. Understanding the relationship between oxygen levels and ROP progression can provide valuable insight into prognostic factors for ROP infants (9).

Both oxygen toxicity and relative hypoxia can contribute to ROP. In other words, exposure to supplemental oxygen itself is a risk factor for premature infants to develop ROP (3, 10). Limiting the use of supplemental oxygen reduces the incidence of ROP, but may increase the risk of other hypoxia-related systemic complications, including death. In a previous study conducted by Rasoulinejad et al., the results indicated that premature infants with ROP have a lower level of partial pressure of oxygen (PO_2) (11). In this research, we investigate the effect of PO_2 and the factors that determine the response rate to the treatment of ROP patients (decrease in stage or increase in zone).

Methods

After being approved by the ethics committee of Babol University of Medical Sciences with code IR.MUBABOL.REC.1399.373, this retrospective cohort study (2010-2020) was conducted in the Neonatal Intensive Care Unit (NICU) of Ayatollah Rouhani Hospital in Babol among 502 premature babies (less than 34 weeks of gestation with a birth weight of less than 2500 grams) (only the results were used and no intervention was done). The inclusion criteria included the presence of ROP in at least one eye and having the mentioned conditions (age and weight) for prematurity. Babies with birth weight less than 2500 grams, gestational age less than 34 weeks and presence of ROP in at least one eye were included in the study, and in case of gestational age more than 34 weeks, birth weight more than 2500 grams, as well as patients with incomplete medical records, they were excluded from the study.

[DOI: 10.22088/jbums.25.1.427]

All eye examinations were performed by an ophthalmologist (vitreoretinal surgeon). Initial examinations were performed at the time of birth (the first day of birth). One hour after the administration of 2.5% phenylephrine and 0.5% tropicamide, fundoscopic examinations were performed using a binocular indirect ophthalmoscope, 28D lens, scleral depressor and pediatric speculum. Babies were examined for ROP and babies with ROP were included in the study.

The zones of ROP were classified as: zone I (zones defined by a circle in the center of the optic nerve), zone II (the zone extending centrifugally from the edge of zone I) and zone III (the crescentic zone remaining from zone II in the anterior retina) (2). Moreover, the stage of ROP was divided into five stages based on the International Classification of Retinopathy of Prematurity (ICROP), which starts with the initial phase and after progression, becomes advanced ROP with bleeding, fibrovascular changes, retinal stretching and retinal detachment (2).

After determining the zone and stage of ROP, laboratory characteristics related to blood oxygen saturation were recorded. Then, regular eye examinations continued and the treatment protocol, including the injection of anti-vascular endothelial growth factor monoclonal antibody, was performed based on ICROP criteria (2). After completion of treatment, patients were reassessed for treatment success (complete cure (absence of ROP) (2), reduction in stage and increase in zone).

Based on the results of the second examination, ROP patients were divided into two categories: completely cured patients (289 people) and other patients (213 people; including people with partial recovery, no change and disease progression). Also, patients for whom complete recovery was not achieved (213 people with partial recovery, people with no change and people with disease progression) were divided into three groups based on the changes in the stage of ROP (stage): reduced disease stage (39 patients), no change (121 patients), and increased disease stage (53 patients). Patients who did not fully recover (213 people; partial recovery, people with no change and people with disease progression) were divided into three groups based on the changes in the affected zone: decrease in the number of disease zone (25 patients), no change (147 patients), and increase in the number of disease zone (41 patients).

Finally, the data were analyzed using SPSS version 22 and Mann-Whitney test to evaluate two-state data and Kruskal-Wallis test to evaluate multi-state data, and $p<0.05$ was considered significant.

Results

Due to the omission of incomplete records in the medical files, out of a total of 828 patients with ROP in the study by Rasoulinejad et al. (11), 502 patients with ROP were included in this study. Out of this number, 193 patients had stage I, 232 patients had stage II, 76 patients had stage III and 1 patient had stage IV. In addition, 55 patients had zone I, 245 patients had zone II and 202 patients had zone III involvement.

The results of the Mann-Whitney test analysis showed that the mean level of PO_2 and oxygen saturation between the two groups of completely cured patients and other patients did not have a statistically significant difference (Table 1). The results of the analysis with the Kruskal-Wallis test showed that the mean level of PO_2 and oxygen saturation between the three groups of people with partial recovery, people without change and people with disease progression show no statistically significant difference (Table 2).

The results of the analysis using the Kruskal-Wallis test showed that the mean level of PO_2 and oxygen saturation between the three mentioned groups did not have a statistically significant difference (Table 3). In addition, in patients who have not fully recovered, the level of PO_2 and oxygen saturation shows no significant relationship with the degree of decrease or increase in stage and zone (Table 4).

[DOI: 10.22088/jbums.25.1.427]

Table 1. Comparison of differences in PO_2 and oxygen saturation in two groups of completely cured patients and other patients

Parameter and group	Mean±SD	p-value
PO_2		
Completely cured patients	73.76±57.75	0.599
Other patients	82.01±66.78	
Oxygen saturation level		
Completely cured patients	78.67±17.79	0.155
Other patients	82.76±18.01	

Table 2. Comparison of differences in PO_2 and oxygen saturation among patients without full recovery

Parameter and group	Mean±SD	Mean score	p-value
PO_2			
Partial recovery	87.10±62.03	28.85	
Unchanged	85.09±68.38	28.56	0.641
Disease progression	73.00±70.31	23.92	
Oxygen saturation level			
Partial recovery	86.13±18.75	24.13	
Unchanged	84.16±14.56	21.62	0.669
Disease progression	75.89±26.74	18.83	

Table 3. Comparison of difference in PO_2 and oxygen saturation in groups based on stage and zone in patients without full recovery

Variable and group	Mean±SD	Mean score	p-value
PO_2 stage			
Partial recovery	86.36±58.89	30.05	
Unchanged	85.09±68.3	28.89	0.599
Disease progression	73.00±70.31	24.15	
Oxygen saturation stage			
Partial recovery	87.00±17.73	24.83	
Unchanged	84.16±14.25	22.00	0.629
Disease progression	75.89±26.74	19.17	
PO_2 zone			
Partial recovery	76.11±59.90	26.17	
Unchanged	83.25±69.96	26.72	0.876
Disease progression	85.25±70.09	30.00	
Oxygen saturation zone			
Partial recovery	86.75±19.20	24.38	
Unchanged	81.73±18.79	20.27	0.666
Disease progression	70.09±10.58	19.33	

[DOI: 10.22088/jbums.25.1.427]

Table 4. Comparison of the difference in PO_2 and oxygen saturation in groups based on the degree of decrease/increase in stage and zone in patients without complete recovery

Variable and group	Mean±SD	Mean score	p-value
PO_2 stage			
Two degrees of increase in stage	89.00±78.26	31.30	
One degree of increase in stage	63.00±68.40	19.69	
Unchanged	85.09±63.36	28.89	0.611
One degree of decrease in stage	91.56±64.07	29.56	
Two degrees of decrease in stage	63.00±22.62	32.25	
Oxygen saturation stage			
Two degrees of increase in stage	97.50±3.53	35.00	
One degree of increase in stage	69.71±27.41	14.64	
Unchanged	84.16±14.26	22.00	0.274
One degree of decrease in stage	86.43±20.23	25.43	
Two degrees of decrease in stage	89.00±7.07	22.75	
PO_2 zone			
Two degrees of increase in stage	63.00±22.62	2.00	
One degree of increase in stage	91.56±64.07	29.19	
Unchanged	85.09±69.38	26.72	0.514
One degree of decrease in stage	63.00±68.39	28.60	
Two degrees of decrease in stage	89.00±78.26	37.00	
Oxygen saturation zone			
Two degrees of increase in stage	89.00±7.07	2.50	
One degree of increase in stage	86.43±20.23	27.50	
Unchanged	84.16±14.25	20.27	0.281
One degree of decrease in stage	69.71±27.41	16.25	
Two degrees of decrease in stage	97.50±3.53	25.50	

Discussion

According to the results of this study, there was no significant difference in PO_2 and oxygen saturation in people with ROP who responded completely to treatment compared to people who did not respond completely to treatment. In the study of Rasoulinejad et al., it was shown that the oxygen level in infants with ROP is significantly lower than those without ROP (11). In other words, insufficient oxygen level leads to retinopathy in premature babies. Therefore, the need for oxygen is higher in ROP babies. Although our results did not show the effect of PO_2 and oxygen saturation regarding response to treatment in ROP patients, a study by Teoh et al., as a similar study in this regard, showed that the duration of oxygen therapy is an effective factor in creating a suitable response to treatment and recovery of infants with ROP (12). In this regard, the study of Higgins showed that PO_2 and oxygen saturation are directly related to the reduction of ROP stage and have no effect on the recovery rate of patients (13).

Our results show that in patients with ROP who do not fully respond to treatment, the level of PO_2 or oxygen saturation has no effect on the treatment process. Although compared to patients without change or with partial improvement, the levels of PO_2 and oxygen saturation were lower in patients whose disease had progressed despite receiving treatment, this difference was not statistically significant. In the study of York et al., PO_2 was introduced as a risk factor in the development of ROP (14). Moreover, in the aforementioned

[DOI: 10.22088/jbums.25.1.427]

study, it was shown that PO_2 fluctuations during NICU hospitalization increase the risk of ROP. The study of Rasoulinejad et al. showed that the amount of PO_2 in ROP patients with zone 1 involvement is higher than in ROP patients with involvement of other zones (11). This suggests that PO_2 is an important indicator of worsening ROP in terms of retinal zone 1 involvement. However, the result of the current study showed that PO_2 and oxygen saturation have no effect on the outcome of the treatment (decreasing or increasing the probability of recovery) in terms of decreasing or increasing the involved zone.

A study by Al-Essa et al. showed that exposure to high oxygen pressure in treatment can be considered as a risk factor in the occurrence of ROP (15). However, our study shows the lack of importance of PO_2 in the chance of treatment success. According to the findings of our study and other studies, oxygen deficiency is effective in causing ROP and oxygen therapy plays an effective role in the treatment of ROP patients, but the amount of oxygen at the beginning of ROP diagnosis is not related to the ROP treatment process.

Despite the undeniable role of hypoxia in the development of ROP, the level of PO_2 and oxygen saturation are not related to the development of complete recovery, partial recovery, reduction of zone and stage of ROP. It is suggested that a study with a larger statistical population investigate the possibility of the relationship between the treatment process of ROP disease and other blood variables such as blood gas, hemoglobin and RBC profile, inflammatory factors and demographic indicators (such as weight, premature birth age, gender, etc.). Furthermore, it is possible to examine the relationship between the role of gene polymorphisms involved in the pathogenesis of ROP, such as the NDP gene, with the rate of response to treatment, as well as changes in stage and zone during the treatment process.

Conflict of interest: The authors declare that there is no conflict of interest.

Acknowledgment

We hereby express our gratitude to the Research and Technology Vice-Chancellor of Babol University of Medical Sciences for supporting the research and colleagues working in the NICU department of Ayatollah Rouhani Hospital.

[DOI: 10.22088/jbums.25.1.427]

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[DOI: 10.22088/jbums.25.1.427]