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REVIEW ARTICLE

Retinopathy of prematurity and its relationship with oxygen therapy: an integrative review

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Abstract

Introduction: Retinopathy of prematurity (ROP) is a disease characterized by abnormal angiogenesis of the immature retina. One of the main causes is inadequate and poorly administered oxygen administration in delivery rooms and/or neonatal intensive care units. **Objectives:** To gather scientific evidence regarding ROP and the use of oxygen therapy, as well as to understand its pathophysiology and possible prevention factors. **Methods:** This is an integrative review. The PubMed, Medline, ScienceDirect, SciELO and Cochrane databases were used, and terms related to ROP were searched in English, French or Portuguese. **Results:** Retinopathy of prematurity is a severe vasoproliferative disease that occurs in premature newborns, which, if not treated in a timely manner, can lead to retinal detachment and visual impairment. Pathophysiologically, complete retinal vascular development, which occurs between the 40-44th week of postmenstrual age, is interrupted due to prematurity. Currently, the main cause of ROP is the misuse of oxygen therapy in newborns, however, there are other factors such as congenital heart disease and anencephaly. **Conclusion:** Advances in neonatal care have allowed an increase in the survival rate in preterm infants and the incidence of ROP has accompanied this increase. Therefore, since the main cause is related to the inadequate use of oxygen therapy, including hyperoxia and fluctuations in oxygen saturation levels, maintaining control of this therapeutic technique is a great artifice against the occurrence of ROP. However, caution is required when decreasing oxygen saturation levels, as this reduction may increase mortality in neonates.

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INTRODUCTION

Retinopathy of prematurity (ROP) is a serious condition that affects preterm infants born before 37 weeks of gestation, characterized by the growth of abnormal blood vessels in the retina.[1] In terms of pathophysiology, it represents an abnormal angiogenesis resulting from the vascularization of an immature retina.[2] ROP can advance to fibrovascular proliferation towards the vitreous, forming membranes and traction bridges that lead to retinal detachment and a reduction in visual acuity to varying degrees.[3]

The primary cause of ROP is inadequate oxygen administration in delivery rooms or neonatal intensive care units.[1] However, several other factors can contribute to the progression of this disease, including patent ductus arteriosus, perinatal asphyxia, intraventricular hemorrhage, sepsis, prolonged parenteral nutrition, and blood transfusions.[3]

METHODS

This is an integrative review. All articles were sourced from public databases, including PubMed, Medline, ScienceDirect, SciELO, and Cochrane. Searches focused on terms related to retinopathy of prematurity, oxygen therapy, premature birth, and newborns. Preference was given to articles published in the last ten years that were freely accessible and available in English, French, or Portuguese. Studies addressing diagnosis, prevention, and various causes of retinopathy of prematurity were selected. The selection was restricted to articles published in highly regarded journals; duplicate, paywalled articles and those published over 20 years ago were excluded. Additional literature not found in these databases was utilized to enhance the general understanding of the modes of action and specific classifications and to illustrate historical descriptions of the condition under investigation. The authors of this article declare that they have no conflicts of interest.

DISCUSSION

Retinopathy of prematurity (ROP) is a severe vasoproliferative disease that occurs in premature infants born before 37 weeks of gestation, affecting the blood vessels of the retina during conceptus development.[1,4] It primarily manifests in preterm newborns, especially those born before 28 weeks of gestation and weighing less than 1,000 grams,[5] as a disruption in the vascularization of the retina. If not detected and treated promptly, ROP can lead to retinal detachment and severe visual conditions[1,6] such as glaucoma, strabismus, myopia, and amblyopia.[6] ROP is one of the leading causes of preventable blindness in children.[4]

ROP's pathophysiology involves delayed retinal vascularization, characterized by the attenuation and obliteration of vessels shortly after birth. Complete retinal vascular development occurs between 40 and 44 weeks of postmenstrual age and is disrupted in cases of prematurity.[6] Also, from 4 to 8 weeks after birth, abnormal proliferation of retinal vascular cells leads to retinal and vitreous neovascularization, which stimulates the avascular peripheral retina due to cellular hypoxia associated with metabolic demand.[6] The hypoxia of the avascular peripheral retina serves as the primary biochemical stimulus that prompts the production of inducible factors in response to low oxygen supply, activating angiogenic genes and stimulating the pathological neovascularization observed in ROP.[6]

The primary cause of ROP is the poorly controlled use of oxygen therapy in newborns within neonatal intensive care units (NICUs). Additional causes of ROP include cyanotic congenital heart disease and anencephaly.[1] Furthermore, risk factors for developing ROP encompass maternal, prenatal, and perinatal elements, demographics, medical interventions, nutrition, and genetics. These factors include low birth weight, low gestational age, prolonged parenteral nutrition, apnea, hypocapnia and hypercapnia, intermittent hypoxemia (SpO2 <80% for one minute or more), fluctuations in oxygen levels, resuscitation with 100% oxygen (early hyperoxia), the number of blood transfusions administered, the number of hours on ventilation, septicemia, among others[1,6] (Table 1).

Table 1. Summary of related factors and consequences of ROP.

	Related Factors	Consequences
Retinopathy of prematurity (ROP)	- Poorly oxygen therapy control; - Low birth weight; - Gestational < 28 weeks; - Intermittent hypoxemia.	- Retinal detachment; - Visual impairment; - Glaucoma; - Strabismus; - Amblyopia.

A meta-analysis by Askie *et al*. (2017), which included five randomized clinical trials, concluded that newborns assigned to the lowest oxygen saturation group (85% to 89%) had a lower incidence of serious diseases, such as ROP and COPD, compared to those in the highest oxygen saturation group (91% to 95%). However, this group also faced a higher risk of death from 18 to 24 months of corrected age.[7]

However, the meta-analysis by Sabri *et al*. (2022) indicated no significant differences in death rates or serious diseases between the higher and lower oxygen saturation groups.[6] It also noted that most systematic reviews, consensus statements, commentaries, and the American Academy of Pediatrics have established a therapeutic oxygen saturation target between 90% and 95%.[6] Preventive measures that can be adopted include administering antenatal corticosteroids between 24 and 35 weeks of gestational age for pregnant women at risk of preterm labor, according to the American College of Obstetricians and Gynecologists (2017);[8] optimizing

parenteral nutrition to prevent hyperglycemia; and controlling pain, infections, and temperature, along with vitamin E supplementation, inositol, and adequate breastfeeding.[6]

Classification of ROP

ROP has a standardized International Classification, first published in 1984, based on location, morphological characteristics, and active and scarring disease severity.[6] In 2021, it was updated to the third version of the International Classification of Retinopathy of Prematurity (ICROP3), which states that the more posterior the disease, the greater the severity and extent of retinal vascular tissue involved.[9] ROP can be classified into four zones and five stages of severity and presence of disease plus, a posterior retinal vascular biomarker. The zones are defined as Zone I, posterior Zone II, the remainder of Zone II, and Zone III, with the first two indicating more severe involvement.[6] The severity of the disease is determined based on the zone, stage, and the tortuosity and dilation of the retinal vessels that develop in the posterior pole of the eyeball, referred to as “pre-plus” or “plus” disease.[10]

Diagnosis

The diagnosis of ROP primarily relies on examining the fundus of the eye.[11] The Brazilian Ministry of Health recommends that all newborns receive the red reflex test (RRT) before discharge and that this test be conducted at least two or three times a year during the first three years of life.[12] Additionally, the Brazilian Society of Pediatric Ophthalmology (SBOP) and the Brazilian Society of Pediatrics (SBP) advise that in premature infants with a gestational age of less than 32 weeks or a birth weight below 1500 grams, the RRT should be performed 30 days after birth and then sequentially as directed by an ophthalmologist.[13]

CONCLUSION

Understanding the mechanisms involved in the pathogenesis of ROP is crucial, as advancements in neonatal care have significantly improved the survival rate of premature infants, among whom the incidence of this condition is higher. Therefore, implementing prevention methods is essential. Since the primary cause of ROP is linked to the improper use of oxygen therapy, specifically hyperoxia and fluctuations in oxygen saturation levels, maintaining control over this therapeutic technique is an effective strategy to prevent the disease. However, caution is necessary when reducing oxygen saturation levels, as such decreases can increase neonatal mortality.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to disclose.

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