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Retinopathy of prematurity: analysis of a damage reduction attempt

Retinopatia da prematuridade: análise de uma tentativa de redução de danos

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Abstract

Objective: *To evaluate the efficacy of an oxygen saturation reduction protocol used to supplement preterm newborns (PTNB) hospitalized in a neonatal ICU to prevent the onset of retinopathy of prematurity (ROP).* ***Methods:*** *This is a cohort study performed in a single Neonatal ICU. The first group (pre-protocol, n = 30) used oxygen with hemoglobin saturation > 95%. Since the institution of a new oxygen therapy protocol that maintained hemoglobin saturation between 90% and 95%, the second group was obtained (post-protocol n = 28). All included preterm infants had a gestational age of less than or equal to 32 weeks and / or birth weight of 1500 g or less, retinal mappings from 28 days of life and follow up for up to 45 weeks of corrected gestational age.* **Results:** *58 cases were studied, excluding those who died (15/58; 26.8%), ROP was diagnosed in 15/43 patients (34.9%). The lower gestational age significantly influenced the appearance of ROP (p = 0.002). Regarding the number of ROP cases and deaths, no statistically significant difference was observed between groups. Oxygen therapy time was significantly associated with the presence of ROP in both groups. Boys were six times more affected by ROP than girls.* ***Conclusion:*** *Reduction of oxygen saturation was not effective in reducing the number of cases of ROP.*

Keywords: *Retinopathy of prematurity; Oxygen inhalation therapy; Intensive care units, neonatal; Infant newborn*

Resumo

Objetivo: Avaliar a eficácia de um protocolo de redução da saturação do oxigênio utilizado na suplementação dos recém-nascidos pré-termos (RNPT) internados em uma UTI neonatal para prevenir o aparecimento da Retinopatia da prematuridade (ROP). **Métodos:** Trata-se de estudo de coorte realizado em única UTI Neonatal. O primeiro grupo (pré-protocolo, n=30) fez uso de oxigênio com saturação de hemoglobina >95%. A partir da instituição de um novo protocolo de oxigenioterapia que manteve a saturação de hemoglobina entre 90% e 95% obteve-se o segundo grupo (pós-protocolo n=28). Todos os RNPT incluídos tinham idade gestacional de menor ou igual 32 semanas e/ou com peso de nascimento igual ou abaixo de 1500g, fizeram mapeamentos de retina a partir de 28 dias de vida e seguimento por até 45 semanas de idade gestacional corrigida. **Resultados:** Dos 58 casos estudados, excluindo-se os que foram a óbito (15/58; 26,8%) dos casos, ROP foi diagnosticado em 15/43 (34,9%) pacientes. A menor idade gestacional influenciou significativamente no aparecimento da ROP (p=0,002). Em relação ao número de casos de ROP e de óbitos não se observou diferença estatisticamente significativa entre os grupos. O tempo de oxigenioterapia foi significativamente associado com a presença de ROP em ambos grupos. Meninos foram seis vezes mais acometidos por ROP que as meninas. **Conclusão:** A redução da saturação de oxigênio não se mostrou eficaz para redução de número de casos de ROP.

Descritores: Retinopatia da prematuridade; Oxigênioterapia; Unidades de terapia intensiva neonatal; Recém-nascido

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Introduction

Retinopathy of prematurity (ROP) affects around 20,000 children per year in Brazil.[1] The incidence of ROP in high-income countries has remained stable over the past three decades, but due to the increased survival of premature babies, the number of children affected by ROP is increasing in low- and middle-income countries1. ROP is a vasoproliferative disease secondary to inadequate vascularization of the retina occuring in preterm newborns (PTNB).[2] It has a multifactorial etiology, and is associated with risk factors such as oxygen saturation, hyperglycemia, blood transfusions, excessive brightness, among others. [2] In some children ROP may develop with inflammation and hemorrhage, which may be followed by fibrotic cicatricial process, retinal detachment and irreversible blindness.[3] In order to detect the highest number of cases with indication of treatment, it is recommended that the first ocular examination in the preterm newborns with birth weight ≤ 1500g and/or gestational age ≤ 32 weeks is done between the 4th and 6th week of life. [4]

Throughout the 1950s, clinical reports and animal studies led to increasing evidence that increased duration and concentration of oxygen use followed by relative hypoxia was a factor causing ROP. [1] The recommendation to minimize the use of oxygen helps preventing ROP. However, underutilization of oxygen in neonates may increase morbidity and mortality in some circumstances.[1,2] Therefore, in neonatal practice, balance is necessary between the risks and benefits of oxygen therapy.

In the present study, the efficacy of the implantation of a new oxygen therapy protocol in which oxygen saturation was reduced with the intention of preventing ocular damage in a Neonatal Intensive Care Unit (NICU) was evaluated.

Methods

The present study was submitted and approved in the ethics committee of the institution under number CAAE 44425815.5.0000.5225. This is a cohort study carried out in a single Neonatal Intensive Care Unit located in Curitiba-PR.

PTNIs with gestational age equal to or less than 32 weeks or with birth weight equal to or less than 1500g were included in the study, with retinal mappings after 28 days of life and follow-up with ophthalmologists for up to 45 weeks corrected gestational age. Patients who had congenital malformation or who came from other services were excluded from the study.

Two groups of NBs were selected for the study. The first group (pre-protocol) used oxygen with hemoglobin saturation > 95% and was hospitalized in the NICU between July 2014 and April 2015. Data from this group was obtained retrospectively. As of June 2015, a new oxygen therapy protocol was instituted in the NICU in a study based on a study carried out in Australia and New Zealand (BOOST II, 2013),(5) where the authors reduced the oxygen saturation used for PTNI in order to minimize damages such as ROP. The new protocol implanted in our NICU aimed to maintain hemoglobin saturation between 90% and 95%. For this purpose the NICU team was trained, and received the following guidelines following the guidelines of the protocol of BOOST II5:

• In oxygen therapy patients, oximeter alarms should be set at a minimum of 89% and a maximum of 96%.

• If the hemoglobin saturation indicated by the oximeter was above 95%, it should decrease FiO2 (inspired oxygen fraction) by 5% every 30 minutes until the saturation reached a level between 90% and 95%.

• If the hemoglobin saturation indicated by the oximeter was below 90%, it should immediately increase FiO2 (inspired fraction of oxygen) by 5% or in an amount at the discretion of the neonatologist on call.

• For patients on mechanical ventilation, the use of the "O2 100%" feature should be avoided for situations of unsaturation, as it induces excessively large fluctuations in FiO2.

• Active withdrawal from mechanical ventilation should be done whenever possible, avoiding hyperoxia.

Since the introduction of this new oxygen therapy protocol, a second study group (post-protocol) was formed, and such data was collected prospectively, including newborns hospitalized in the NICU between July 2015 and March 2016. The children studied in both groups were followed up to 45 weeks of age. Additionally, the time of exposure to oxygen therapy in the groups studied was evaluated.

The diagnosis of ROP was made according to the Guidelines for the Screening of Detection and Treatment of ROP. (5,6) Tests for the early detection of ROP were carried out in all PTNI with birth weight ≤ 1,500 grams and/or GA ≤ 32 weeks at birth.

All PTNI included in the study had the medical procedures, medications used, and the intercurrences recorded. Ophthalmologic examination with indirect binocular ophthalmoscopy was carried out in all 6-week-old patients, after dilation of the pupils using tropicamide 0.5% and phenylephrine 2.5% eyedrops, instilling one drop every 10 minutes three times approximately 1 hour before the examination. A 28-diopter lens with blepharostat for Storz's newborn was used to provide an adequate view of the extreme periphery of the retina in the 360° without the routine use of scleral depression. The ophthalmologic examination was carried out by the same ophthalmologist for all cases at the neonatology center.

The 1984 ROP international classification[6,7] stratified the disease according to severity in five stages [1-5], location in three zones (I-III), and extension in hours (1-12 h). The disease is characterized by arteriolar dilation and venous tortuosity, which would be an indicator of disease activity. The description of these findings is as follows: Stage 1: peripheral retinal ischemia and presence of a demarcation line between the vascularized retina and the ischemic retina; Stage 2: presence of a raised ridge over the peripheral region of the retina; Stage 3: presence of retinal or extraretinal fibrovascular proliferation on raised ridges; Stage 4: onset of partial peripheral or central tractional retinal detachment (stages 4A or 4B); and Stage 5: total retinal displacement. [6,7]

Statistical analysis

Data was tabulated and expressed by medians, averages and standard deviations or by frequencies and percentages. Statistical analysis was carried out using the statistical

software Prism 5.0 (GraphPad Prism, California, USA). The Kolmorov-Smirnof test was used to verify the normality of the data. Continuous variables were compared with the t- or Mann-Whitney tests; categorical variables were expressed as percentages and compared with the chi-square test or Fisher's exact test, as appropriate. P-values lower than 5% were considered significant.

Results

Of the 58 cases studied, excluding patients who died (15/58 -26.8%), ROP was diagnosed in 15/43 patients (34.9%) who survived 45 days and could be evaluated. The GA had a significant influence on the onset of ROP, and the patients who had the disease had an average GA of 27.6 ± 2.74 weeks, and those who did not 29.9 ± 2.17 weeks (p = 0.002). Still regarding gestational age, 16/58 (27.6%) of cases had GA lower than 28 weeks. Of these, 10/16 died, 3/6 (50%) presented ROP, and the other half of patients did not develop ROP.

Birth weight was also significantly lower in patients with ROP than in those without ROP (970.9 ± 264.55g vs 1173.5 ± 187.49g) respectively (p = 0.008). No significant association was found with variables related to pregnant women and intercurrences during pregnancy. Regarding the other findings in the PTNI, no association was found between ROP and variables such as presence of infection, blood transfusion, hypoglycemia and jaundice.

When subdivided, the first group consisted of 30 patients who were part of the pre-protocol group. After the adoption of the new oxygen therapy protocol, 28 patients who had controlled oxygen saturation were evaluated and formed the post-protocol group. Patient data is available in table 1. Regarding the frequency of ROP cases and the occurrence of deaths, no significant difference was observed between the groups. The pre-protocol group had 9 (30%) cases of ROP and 8 (26.7%) cases of death. In the post-protocol group, 6 (21.4%) cases of ROP and 7 (25%) cases of death were found. There was no difference between the classes of ROP observed in the groups. No patient presented ROP class 4 or 5.

Regarding the time of oxygen supplementation, all patients with ROP and patients non-affected were grouped together, and a significant association was observed between longer oxygen therapy and ROP onset. In the pre-protocol group, patients with ROP had an average of 42 days (between 10 and 169 days) with oxygen supplementation, whereas the RNs who did not have the disease had a median of 26 days (between 6 and 51 days, p = 0.06). In the post-protocol group, patients with ROP had a median of 63.5 days (between 15 and 105 days) of oxygen therapy; and those without ROP had a median of 7 days (between 1 and 72 days, p = 0.015).

In addition, it was verified that ROP was more frequent in males. In both groups, it was found that 44% (11/25) of the boys and 12.9% (4/31) of girls were affected (p <0.0001, OR = 6.0, CI = 4.7-18.8).

Discussion

It is known that the oxygen supplementation performed is necessary for PTNI care. However, such a measure can contribute decisively to the occurrence of ROP. If on the one hand it is important to decrease the days of oxygen use and its saturation, on the other hand, such a measure can increase mortality. The present study followed PTNI who were submitted to a lower oxygen saturation to verify a NICU in Brazil, and shows that the decrease in oxygen saturation could not significantly reduce the incidence of ROP.

The frequency of ROP observed in our sample (25.8%) is similar to that described in studies carried out in southern Brazil[8,9] and elsewhere in the world. [10] Factors already described in the literature such as birth weight and GA were significantly associated with the onset of ROP in our study. Carrion et al.[10] in a study carried out in Latin America demonstrated a prevalence variation between 6.6 and 82% for some stage of ROP, and between 1.2 and 25% for severe ROP. Demir et al.[11] demonstrated that around 50% of PTNI with GA lower than 28 weeks of age presented ROP in Turkey, similar to our study, confirming the need to investigate ROP in developing countries.

In our study, the reduction in oxygen saturation for the range of 90-95% did not significantly decrease the incidence of ROP. A randomized study in the United Kingdom, Australia, New Zealand, Canada and the United States in 2013 with 2448 PTNIs of less than 28 weeks of gestational age, one group of patients was maintained in saturation between 85% and 89%, whereas the other was among 91% e 95%.[5] The reduction in the incidence rate of ROP in the group submitted to lower saturation (17.9% vs 8.6%, p <0.001) was observed, but it increased the mortality rate (15.9% vs 23.1%, p = 0.002). [5] Another study carried out in the United States evaluated

Table 1
Pairing characteristics and results of pre-protocol and post-protocol groups.

	Pre-protocol group (n = 30)	Post-protocol group (n = 28)	P-value
Weight (average ± SD)	1061.8 ± 239.09	1090.7 ± 278.18	0.67
Gestational Age –median (interval)	30 (between 23 e 36 weeks)	29 (between 24 e 35 weeks)	0.40
Female gender	12/30 (40%)	14/28 (50%)	0.62
Death	8/30 (26. 7%)	7/28 (25%)	0.88
Retinopathy of prematurity*	9/22 (40.1%)	6/21(28.5%)	0.52
Class 1	3/9 (33.3%)	3/6 (50%)	0.62
Class 2	3/9 (33.3%)	1/6 (16.7%)	0.59
Class 3	3/9 (33.3%)	2/6 (33.3%)	1.0

* Evaluation was only possible in patients who survived.

1316 PTNIs in two groups submitted to different levels of oxygen saturation. [12] The groups compared (85-89% vs 91-95%) did not present a significant difference in the incidence rate of severe ROP (28.3% vs 32.1%, p = 0.21), but the group submitted to the lowest level of oxygen saturation had a higher mortality rate (16.2% vs 19.9% p = 0.04).[12] In the present study, the oxygen therapy protocol aimed at maintaining hemoglobin saturation at a minimum of 90% and a maximum of 95% was not effective in reducing the incidence of ROP. However, due to caring not to reduce oxygen any further, there was no increase in the mortality rate between the groups. This data was corroborated by a meta-analysis study published in 2017, where the authors concluded that there are no differences between oxygen saturations in premature newborns from 85 to 89% and 91 to 95% regarding complications such as bronchopulmonary dysplasia, ROP and cerebral palsy, with only an increase in mortality. [13]

Regarding the time of use of oxygen therapy, it was observed that in both groups a positive association was observed between the onset of ROP in PTNI among those who stayed longer in oxygen use. Hyperoxia triggers vasoconstriction, vascular obliteration, peripheral ischemia, and definitive discontinuation of retinal vascular formation. When maintained for a longer period of time, hyperoxia still leads to an overproduction of vascular endothelial growth factor (VEGF), which stimulates unwanted neovascularization of the retina and the onset of other complications of ROP. [14,15]

It was also found in our study that boys were significantly more affected for ROP, with a ratio of 3:1 cases in boys for each affected girl, with a risk six times higher. This is controversial in the literature. Shim et al.[16] in a study in the Korean population, and Ito et al. [17] in Japan reported no significant differences between genders. On the other hand, Slidsborg et al. [18] found in a study carried out in Finland that males show a two-fold increased risk of onset of ROP. Other national studies on the subject have not found such a difference. [8,9]

The development of ROP in PTNIs is multifactorial. During the last decade, independent studies have documented that prematurity, hyperoxia, growth retardation (intrauterine / postnatal), early postnatal hyperglycemia, among others are risk factors for ROP. (2,15) The NICU team should be informed and work to try to minimize the risks for the development of ROP, among others trying to reduce the time of oxygen therapy in patients.

The data found are in agreement with the current literature; however, it presents limitations due to the sample size. The strength of the study lies in the discussion about bedside care, which should be protocolized and/or individualized, the need for paradigm shifting, the team's understanding of the importance and relevance of the problem - ROP. Increasing the survival of premature newborns who are becoming more premature may further increase the incidence of ROP cases, and further attempts to reduce harm will be required.

Finally, our study concluded that maintaining hemoglobin saturation between 90% and 95% in oxygen therapy of PTNIs with a gestational age of 32 weeks or less and/or birth weight at or below 1500g was not efficient to prevent ROP. In addition, gestational age, birth weight, male gender and the time of oxygen therapy to which the newborn is subject are risk factors for the onset of the disease.

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