Original Article

Factors associated with the use of oxygen therapy and ventilatory support in premature newborns

Fatores associados ao uso de oxigenoterapia e suporte ventilatório em recém-nascidos prematuros

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ABSTRACT | INTRODUCTION: Supplemental oxygen therapy reduces hypoxia by reducing mortality among preterm newborns (PTNBs), but excessive exposure to oxygen has the potential to affect and damage multiple organs of the newborn. **OBJECTIVE:** To determine the factors associated with the use of ventilatory support/oxygen therapy in PTNBs. **MATERIALS AND METHODS:** This is an observational, longitudinal, prospective quantitative study, conducted from July 2019 to March 2020, in a neonatal intensive care unit (NICU) of a public university hospital. PTNBs on oxygen therapy were observed from the time of admission to discharge, and gestational data, birth data and oxygen therapy parameters were collected. **RESULTS:** 62 PTNs were followed with a mean gestational age (GA) of 30.5 weeks (±3.43) and median birth weight (BW) of 1,390 grams (555 g - 3,115 g). The mean hospital stay of 35 days (3-176) and oxygen therapy was 7.5 days (1-176). When relating the total days in oxygen therapy with the value of Apgar at the 5th minute, there was no significant relationship (rho= -0.158; p=0.219), however, there was a relationship with GA at birth (rho= -0.725; p<0.001), use of antenal corticosteroids (p=0.006) and exogenous surfactant (<0.001). There was also a relationship with bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) (p<0.001). **CONCLUSION:** The factors associated with time and use of oxygen therapy were GA, BW, use of antenal corticosteroids and exogenous surfactant, and association with BPD and ROP was also observed.

KEYWORDS: Premature. Neonatal Intensive Care Unit. Ventilatory support Oxygen therapy.

RESUMO | INTRODUÇÃO: A terapia com oxigênio suplementar reduz quadros de hipóxia, diminuindo a mortalidade entre recém-nascidos prematuros (RNPT), porém a excessiva exposição ao oxigênio tem o potencial de atingir e danificar múltiplos órgãos do neonato. **OBJETIVO:** Determinar os fatores associados ao uso de suporte ventilatório/oxigenoterapia nos RNPT. **MATERIAIS E MÉTODOS:** Estudo observacional, longitudinal, prospectivo de caráter quantitativo, realizado no período de julho de 2019 a março de 2020, em unidade de terapia intensiva neonatal (UTIN) de um hospital público universitário. Foram observados RNPT em uso de oxigenoterapia, desde o período de admissão até a alta, sendo coletados dados gestacionais, de nascimento e parâmetros da oxigenoterapia. **RESULTADOS**: 62 RNPT foram acompanhados com média de idade gestacional (IG) de 30,5 semanas (±3,43) e mediana de peso ao nascimento (PN) de 1.390 gramas (555 g - 3.115 g). O tempo médio de internação de 35 dias (3-176) e de oxigenoterapia foi de 7,5 dias (1-176). Ao relacionar o total de dias em oxigenoterapia com o valor do Apgar no 5º minuto, não houve relação significativa (rho= -0,158; p=0,219), porém, houve relação com a IG ao nascimento (rho= -0,725; p<0,001), uso de corticoide antenal (p=0,006) e surfactante exógeno (<0,001). Houve relação também com displasia broncopulmonar (DBP) e retinopatia da prematuridade (ROP) (p<0,001). **CONCLUSÃO:** Os fatores associados ao tempo e uso de oxigenoterapia foram a IG, PN, uso de corticoide antenal e surfactante exógeno, sendo observado também associação com DBP e ROP.

PALAVRAS-CHAVE: Prematuro. Unidade de Terapia Intensiva Neonatal. Suporte Ventilatório. Oxigenoterapia.

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Introduction

Supplemental oxygen therapy is widely used in NICU for the treatment of hypoxia, reducing postnatal mortality and severe disorders caused by lack of oxygen, such as heart failure, pulmonary hypertension and brain damage.[1,2] However, like other medications, oxygen must be given in the correct way, according to the patient's needs[3], because the oxygen supply in high amounts and for prolonged time can lead to hyperoxia, and premature are especially susceptible to this toxicity due to their limitations in the antioxidant defense system, which has the function of inhibiting and/or reducing the damage caused by the action of free radicals.[1,2,4]

The choice of modality to be used in each patient is also of great importance for the success of the therapy.[1] There are different methods, invasive and noninvasive, to perform oxygen delivery. Non-invasive methods include nasal catheters, oxygen helmets (HOOD) and non-invasive ventilation such as continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (NIPPV). In addition to these modalities, oxygen can also be offered through invasive mechanical ventilation.[5]

Excessive oxygen exposure has the potential to affect and damage multiple neonate organs, such as eyes and lungs, and can cause brain bleeds and increased oxygen dependency during hospitalization and at discharge, some of the most frequent complications being DBP and ROP.[2,3]

Due to the benefits and harms generated by the use of oxygen therapy and considering the importance of this therapy in the survival of prematures, it is important to analyze the factors associated with the time of use of oxygen therapy in this population. Therefore, the aim of this study is to determine the factors associated with the use of ventilatory support and oxygen therapy, as well as their relationship with gestational characteristics and health conditions of PTNBs admitted to the NICU of a public university hospital.

Methods

This is an observational, longitudinal, prospective study of a quantitative nature.[6] The study population was composed of premature neonates (born before 37 completed weeks of pregnancy) admitted to the NICU who used ventilatory support/oxygen therapy during hospitalization. With approval by the Ethics Committee for Research Involving Human Beings under opinion 91754318.6.0000.0096, data collection was initiated.

All PTNBs born in the obstetric center of the hospital and admitted to the NICU who used ventilatory support/oxygen therapy for at least 24 hours during the period July/2019 to March/2020 were included in the sample. NBs transferred from hospital or who died during hospitalisation were excluded from the study.

Data collection started on the first day of use of ventilatory support/oxygen therapy of the NB, regardless of the modality offered. Personal and birth data were collected (GA, PN, Apgar score at 5th minute, use of antenatal corticoid and exogenous surfactant). Patients were followed up to hospital discharge and the total number of days in each modality of oxygen therapy (invasive mechanical ventilation, non-invasive mechanical ventilation and inhaled oxygen), the total number of days in use of ventilatory support/oxygen therapy (encompassing all modalities), total days of NICU stay and comorbidities associated with the use of oxygen therapy (BPD and ROP) were recorded.

Data were tabulated in a Excel spreadsheet. Subsequently, they were analyzed using the IBM SPSS 20.0 software. Being performed the Kolmogorov-Smirnov test to evaluate data normality, descriptive tests to characterize the sample profile and Spearman's test to measure the degree of correlation between the variables ventilatory/oxygen therapy modality (days in use of ventilatory support/oxygen therapy, number of days in each modality), the variables related to the NB (GA, PN, Apgar score at the 5th minute) and the health conditions (BPD and ROP). A value of $p<0.05$ was used as significant.[7]

Results

In the collection period, 254 hospitalizations were registered in the NICU. Of these, 62 NB were eligible for participation in the study (NB with GA < 37 weeks and using ventilatory support/oxygen therapy), 35 (56.45%) were male. The mean GA at birth of the sample was 30.5 weeks (±3.43) and the median birth weight was 1,390 g (555 g-3,115 g).

Regarding the classification of prematurity, 16 (25.8%) were classified as late premature (34 to <37 weeks), 12 (19.35%) as moderate premature (32 to <34 weeks), 20 (32.25%) very premature (28 to <32 weeks) and 14 (22.58%) were extremely premature (<28 weeks).

The mean length of hospital stay was 35 days, with a minimum of three days and a maximum of 176 days. The mean time spent ventilatory support/oxygen therapy was 7.5 days ranging from one to 176 days, and two patients were discharged from the NICU to the home still using oxygen therapy via nasal catheter.

In the Apgar score at the 5th minute of birth, 49 (79%) scored above seven, 11 (17.7%) scored from four to six and two (3.2%) scored below three. When relating the Apgar value at the 5th minute with the total number of days using ventilatory support/oxygen therapy, there was no significant relationship (rho= -0.158; p=0.219).

The PTNB analyzed were submitted to different modes of ventilatory support/oxygen therapy, and more than one way can be used according to their clinical need during the hospitalization period. The modalities observed in the study were: invasive mechanical ventilation (IMV) in 64.51%, noninvasive ventilation (intermittent positive nasal pressure – NIPPV; continuous positive airway pressure - CPAP; CPAP bubbles -BCPAP) in 82.25%, and inhalation through oxygen helmet (HOOD) and oxygen nasal catheter (CNO2) in 67.74%.

Table 1 shows some of the characteristics of the sample according to the classification of prematurity.

Table 1. Characteristics of the sample according to the classification of prematurity

	Late premature	Moderate premature	Very premature	Extreme premature
Birth weight	2,302.1g (±504,8)	1,911.6g (±468.6)	1,262g (±298,6)	771g (±150,6)
Days in MV	3 days (1-5)	1 day (1-5)	4 days (1-35)	19 days (2-47)
Days in NMV	2 days (1-6)	2 days (1-12)	7 days (2- 31)	21 days (12-54)
Days on O_2 inhalation	3 days (1-21)	2 days (1-11)	3 days (1-40)	28 days (11-91)
Total days on oxygen therapy	3.5 days (1-21)	2.5 days (1-16)	9.5 days (2-72)	66 days (17-176)
Total days of hospitalization	11.5 days (3-90)	17.5 days (8-47)	40 days (18-94)	51 days (51-176)
GA end of O_2	36,5 (±4,7)	33,1 (±1,1)	33,1 (±3,3)	35,1 (±3,53)
Weight at end of O_2	2,345.6g (±547.1)	1,848.6g (±438.8)	1,659.2g (±470,7)	1,971.7g (±556,2)

Legend: MV: mechanical ventilation; NIV: non-invasive ventilation; O2: oxygen. Values of birth weight, GA end of O2 and weight at the end of O2 described in mean and standard deviation; other values described in median and minimum and maximum values.

There was a relationship between GA at birth and the number of days in IMV (rho= -0.538; p<0.001), NIV (rho= -0.827; p<0.001) and inhaled O2 (rho= -0.634; p<0.001), and the lower the gestational age, the greater the number of days in use of these modalities. When relating to the total number of days on ventilatory support/ oxygen therapy, a relationship (rho= -0.725; p<0.001) was also observed, and the extreme premature infants (born before 28 weeks of GA) remained longer on MV (rho=0.524; p=0.001), NIV (rho= 0.785; p<0.001) and inhaled O2 (rho= 0.583; p<0.001), as seen in table 2.

Table 2. Mean time on each oxygen therapy support according to the prematurity classification

	IMV		**VNI** (NIPPV + CPAP + BCPAP)		**O2 inhalation** (HOOD+CN)	
	N (n%)	Days Median	N (n%)	Days Median	N/NN (n%)	Days Median
Late premature	9 (18%)	3 (1-5)	8 (12%)	2 (1-6)	7 (12,2%)	3 (1-21)
Moderate premature	7 (14%)	1 (1-5)	11 (18,6%)	2 (1-12)	7 (12,2%)	2 (1-11)
Very premature	11 (22%)	4 (1-35)	18 (30%)	7 (2-31)	15 (26,3%)	3 (1-40)
Extreme premature	13 (26%)	19 (2-47)	14 (23,7%)	21 (12-54)	13 (22,8%)	28 (11-91)

Legend: IMV: invasive mechanical ventilation; NIV: non-invasive ventilation; O2: oxygen, N: sample value.
N values described in absolute and relative frequency; other values described in median and minimum and maximum values.

Of the sample, 31 (50%) of the cases used antenatal corticosteroids and 26 (41.9%) used exogenous surfactant after birth. Table 3 shows the characteristics of the sample that used corticosteroids/surfactants regarding GA at birth, birth weight, total days on oxygen therapy and total days of hospitalization, and those who used corticosteroids and surfactants had lower GA and lower BW and had a higher number of days on oxygen therapy and hospitalization.

Table 3. Characteristics of the sample that used antenatal corticosteroids and exogenous surfactant

	No Corticoid	**With Corticoid**	***P value***	**No Surfactant**	**With Surfactant**	***P value***
IG at birth	32,4 (± 2,98)	28,6 (±2,81)	*<0.001**	31,8 (± 2,94)	28,6 (±3,28)	*<0.001**
Birth weight	1.940g (690g-3115g)	1,215g (555g – 2410g)	*0,001**	1.960g (690g-3115g)	987g (555g – 2875g)	*<0.001**
Total days on oxygen therapy	5.5 days (1-69)	14 days (1-176)	*0,006**	4 days (1-69)	42.5 days (1-176)	*<0.001**
Total days of hospitalization	23 days (3-93)	41 days (8-176)	*0,003**	28 days (3-91)	68 days (9-176)	*0,003**

Legend: GA: gestational age; GA values described in mean and standard deviation; other values described in median and minimum and maximum values.
*significant p-value for Spearman's correlation test (p<0.05).

When analyzing the use of antenatal corticosteroids with the modalities of ventilatory support and oxygen therapy, one can observe a relationship with the use of NIV (Phi= 0.362; p=0.005) and inhaled O2 (Phi= 0.291; p=0.023) postnatal. The relationship between surfactant use with the modalities of ventilatory support and oxygen therapy showed a significant relationship with the use of IMV (Phi=0.415; p<0.001) and inhaled O2 (Phi= 0.390; p=0.002). There was no relationship between the use of surfactant and the use of NIV (Phi=0.113; p=0.377).

Of the total sample studied, 11 (17.7%) newborns had a diagnosis of BPD and 9 (14.5%) had a diagnosis of ROP. All had GA at birth less than 32 weeks. There was a significant relationship between BPD and ROP with the use of oxygen therapy, both with modalities and with time of use (Table 4). Of these newborns, three had a diagnosis of the two comorbidities, namely, extreme premature newborns who remained on oxygen therapy for more than 50 days.

Table 4 shows the number of newborns who had BPD, ROP and their characteristics regarding birth and use of oxygen therapy.

Table 4. Characteristics of newborns with BPD and ROP regarding birth data and use of oxygen therapy

	BPD	*P value*	ROP	*P value*
GA at birth	26 weeks (±1.36)	*0,001**	26 weeks (±1.53)	*<0.001**
Birth weight	786.8g (±172.7)	*0,001**	785.5g (±177.05)	*<0.001**
Days MV	35 days (1-47)	*0,008**	31 days (7-47)	*<0.001**
Days NIV	23 days (12-54)	*0,001**	21 days (12-54)	*<0.001**
Days O_2 inhalation	39 days (14-91)	*<0.001**	25 days (15-91)	*<0.001**
Total days of oxygen therapy	72 days (30-176)	*<0.001**	62 days (50-176)	*<0.001**
Total days of hospitalization	91 days (61-176)	*<0.001**	85 days (62-176)	*<0.001**
GA corrected end oxygen therapy	37 weeks (±2.35)	*0,217*	36 weeks (±3.39)	*0,181*
End weight oxygen therapy	2,168g (±403.5)	*0,812*	1.963g (±438)	*0,772*

Legend: BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity; GA: gestational age; MV: invasive mechanical ventilation; NIV: noninvasive ventilation; O2: oxygen. GA values at birth, birth weight, corrected GA end oxygen therapy and end oxygen therapy weight described in mean and standard deviation; values of days in MV, NIV, O2 inhaled, total days of oxygen therapy and hospitalization described in median and minimum and maximum value.
*significant p-value for Spearman's correlation test (p<0.05).

Discussion

This study found that the lowest GA and BW, the use of antenatal corticosteroids and exogenous surfactant were factors associated with the need for ventilatory support/oxygen therapy in PTNBs admitted to the NICU. And the prolonged use of IMV, NIV and inhaled oxygen was related to the development of BPD and ROP.

According to data from the Ministry of Health, prematurity and low weight increase the risk for morbidity and mortality and are risk factors associated with the use of oxygen.[1] Knowing the factors associated with the time and use of ventilatory support and oxygen therapy allows a better management and minimizes the risk of future complications caused by the misuse of oxygen.[1,2,4] In our study, these factors were GA, BW, use of antenal corticosteroids and exogenous surfactant after birth.

The mean GA at birth of the newborns analyzed was 30.5 weeks, classified as very premature, and the median birth weight of the sample studied was 1,390 g, considered very low birth weight. That is, there was a trend that the lower the GA and birth weight, the greater the number of days on oxygen and hospitalization in the NICU. Corroborating the data, the administration of supplemental oxygen in the first hours of life has a great influence on the development and future of this baby. Both hypoxia and hyperoxia are harmful to this organism that is still in development. Insufficient oxygenation can lead to problems in the central nervous system, for example, and oxygenation beyond the required limits can lead to lung and retinal injury.[8,9]

Other factors that interfere with the time and use of oxygen therapy are the modalities of respiratory support. NIV was the most used modality among premature infants in our study (82.25%), followed by IMV (64.51%). Currently, knowledge of the complications related to the use of IMV in premature newborns, especially in extremely premature newborns, has led to the use of NIV as the first therapeutic option, or to a reduction in the time of IMV.[10,11] Recent studies show that noninvasive methods are able to minimize the chance of using IMV and thus reduce lung injury.[10,12]

Some studies show that infants of lower weight and gestational age are exposed to more days in IMV and receive a higher fraction of inspired oxygen.[13] However, in our study, NIV was the most used modality among premature infants (82.25%), followed by IMV (64.51%). This probably occurred because, despite the profile of the population, knowledge of the complications related to the use of IMV in premature infants, especially in extremely premature infants, led to the use of NIV as the first therapeutic option, or to a reduction in the time of IMV.[10,11]

A literature review conducted by Guedes et al.[14] showed the occurrence of 15 different types of deleterious effects associated with the use of IMV (BPD, IMV-associated pneumonia and induced lung injury). Moreover, IMV is a process that involves pain, stress and distress to the NB, which can have consequences for the neurological development that is still under development.[1] Weaning and extubation as early as possible of these patients are important to minimize such complications caused by the use of IMV.[15]

The duration of oxygen use as well as hospitalization time were directly proportional to the group that received antenatal corticosteroids and exogenous surfactant. This finding can be explained due to the clinical indications of these therapies, with antenatal corticosteroid therapy used for fetal lung maturation in premature births that were previously known, and postnatal exogenous surfactant therapy being used for treatment of respiratory distress syndrome. That is, they are therapies that serve to prevent and treat postnatal pulmonary dysfunctions in a population in which pulmonary development is still immature.[16,17]

The most relevant pathologies related to prematurity, such as ROP and BPD, are associated with the use of oxygen supplementation and the immaturity of the antioxidant defense system in the postnatal period.[18] Of the 62 PTNBs analyzed, 17.7% were diagnosed with BPD and 14.5% with ROP. When analyzing the characteristics of the two groups, it can be observed that they were formed by extremely premature newborn infants (mean GA of 26 weeks), and extremely low birth weight (BW <1,000g).

In addition, PTNBs with BPD and ROP were those who remained for a longer period of days in the use of O2 and had a longer period of hospitalization. These findings corroborate the data already found in the literature.[19-21] Higgins[21], described in his article that ROP affects newborns with low GA and low birth weight. Lima[19] also found an incidence of BPD inversely proportional to BW, that is, NB with low BW had a higher incidence of BPD.

Analyzing our results and comparing data from studies conducted in other NICUs, we observed that our center presented a lower percentage of incidence of comorbidities such as ROP and BPD. In the study by Xavier[22], 26% of the PTNBs evaluated had ROP, and 77.4% used surfactant. However, it is noteworthy that in this study only PTNBs and low birth weight PTNBs were evaluated. The study by Tapia[23] determined the incidence of BPD in a sample of 107 very low birth weight premature newborn PTNBs and resulted in an incidence of 39.3%, being inversely proportional to gestational age, as found in our study.

Knowing the role of oxygen therapy in the studied population, its benefits and its possible complications, it is necessary to discuss more frequently how to improve ventilatory strategies to reduce the time of use of IMV and oxygen therapy in PTNBs, as this approach will impact the future quality of life of these NBs.[24] However, a limitation/bias that can be pointed out in this study is the fact that it was a unicenter study. Multicenter studies may be necessary to show the reality of more heterogeneous populations.

With the results of this study, it can be concluded that the factors associated with the use of ventilatory support and oxygen therapy in preterm infants were the lower GA and the lower BW, as well as the gestational history of antenatal corticosteroid use and need for exogenous postnatal surfactant. In addition to these factors, health conditions (BPD and ROP) were related to longer use of ventilatory support and oxygen therapy. These findings complement the studies already found in the literature and confirm the importance in the care of the implementation and management of supplemental oxygen in NB, especially in premature infants.

Conflicts of interest

No financial, legal or political conflicts involving third parties (government, companies and private foundations, etc.) have been declared for any aspect of the submitted work (including but not limited to grants and funding, participation in advisory board, study design, manuscript preparation, statistical analysis, etc.).

Authors' contributions

Espíndola CS carried out the collection, data analysis, writing of the project and article. Andreazza MG participated in the collection, data analysis, assistance and correction of the manuscript. Zechim FC collaborated in the collection, data analysis and assistance in the preparation of the manuscript. Jurkevicz R worked on the data collection and writing of the project. Takeda SYM and Sarquis ALF assisted and corrected the manuscript.

References

1. Soares LG, Sauka JM, Higarashi IH, Soares LG, Filipin LCS, Uema RTB. Effects of oxygenotherapy in neonatology: integrating literature review. Rev enferm atual in derme. 2019;87(25). https://doi.org/10.31011/reaid-2019-v.87-n.especial-art.165

2. Kayton A, Timoney P, Vargo L, Perez JA. A Review of Oxygen Physiology and Appropriate Management of Oxygen Levels in Premature Neonates. Adv Neonatal Care. 2018; 18(2):98-104. https://doi.org/10.1097/ANC.0000000000000434

3. Walsh BK, Smallwood CD. Pediatric Oxygen Therapy: A Review and Update Brian. Resp Care. 2017;62(6):645-661. https://doi.org/10.4187/respcare.05245

4. Deuber C, Terhaar M. Hyperoxia in very preterm infants: A systematic review of the literature. J. Perinat Neonat Nurs. 2011;25(3):268-274. https://doi.org/10.1097/jpn.0b013e318226ee2c

5. Cherian S, Morris I, Evans J, Kotecha S. Oxygen therapy in preterm infants. Paediatr Respir Rev. 2014; 15(2):135-41. https://doi.org/10.1016/j.prrv.2012.12.003

6. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Delineando a pesquisa clínica. 4a ed. Porto Alegre: Editora Artmed; 2015.

7. Portney LG, Watkins MP. Foundations of clinical research: applications to practice. 3 a ed. Philadelphia: F.A. Davis Compan; 2015.

8. Jobe AH, Goldenberg RL. Antenatal corticosteroids: an assessment of anticipated benefits and potential risks. Am. J. Obstet. Gyneco. 2018;219(1):62-74. https://doi.org/10.1016/j.ajog.2018.04.007

9. Thomsom L, Paton J. Oxygen Toxicity. Paediatr. Respir. Rev. 2014;15(2): 120-3. https://doi.org/10.1016/j.prrv.2014.03.003

10. Shi Y, Muniraman H, Biniwale M, Ramanathan R. A Review on Non-invasive Respiratory Support for Management of Respiratory Distress in Extremely Preterm Infants. Front Pediatr. 2020;8:270. https://doi.org/10.3389/fped.2020.00270

11. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, te Pas A, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome. Neonat. 2019;115(4):432-450. https://doi.org/10.1159/000499361.

12. Sarmento GJV. Fisioterapia respiratória em pediatria e neonatologia. 2ª ed. São Paulo: Manole; 2011.

13. Shalish W, Kanbar L, Kovacs L, Chawla S, Keszler M, Rao S, et al. The Impact of Time Interval between Extubation and Reintubation on Death or Bronchopulmonary Dysplasia in Extremely Preterm Infants. J Pediatr. 2019;205(2):70-76. https://doi.org/10.1016/j.jpeds.2018.09.062

14. Guedes JM, Conceição SL, Albergaria TFS. Deleterial effects of invasive mechanical ventilation in prematures: systematic review. Rev Pesq Fisio. 2018;8(1):119-130. https://doi.org/10.17267/2238-2704rpf.v8i1.1772

15. Ancora G, Lago P, Garetti E, Pirelli A, Merazzi D, Pierantoni L, et al. Follow-up ar the corrected age off 24 months of preterm newborns reveiving continuous infusion of fentanyl for pain control during mechanical ventilation. J. Pain. 2017;158(5):840-45. https://doi.org/10.1097/j.pain.0000000000000839

16. McPherson C, Wambach JA. Prevention and Treatment of Respiratory Distress Syndrome in Preterm Neonates. Neonat Net. 2018;37(3):169-177. https://doi.org/10.1891/0730-0832.37.3.169

17. Blankenship SA, Brown KE, Simon LE, Stout MJ, Tuuli MG. Antenatal Corticosteroids in Preterm Small-for-Gestational Age Infants: A Systematic Review and Meta-Analysis. Am J Obstet Gynecol MFM. 2020;2(4):100215. https://doi.org/10.1016/j.ajogmf.2020.100215

18. Torres-Cuevas I, Parra-Llorca A, Sánchez-Illana A, Nuñez-Ramiro A, Kuligowski J, Cháfer-Pericás C, et al. Oxygen and oxidative stress in the perinatal period. Red Biol. 2017;12:674-681. https://doi.org/10.1016/j.redox.2017.03.011

19. Lima MRO, Andrade MA, Araújo APG, Figueroa JN, Andrade LB. Influence of maternal and neonatal factors on bronchopulmonary dysplasia development. Rev. Assoc. Med. Bras. 2011;57(4):398-403. https://doi.org/10.1590/S0104-42302011000400012

20. Silva GAA, Annes ALM, Pisco MDBV, Silva RM. Displasia Broncopulmonar: definição, fisiopatologia e tratamento: revisão da literatura. Inov Saúd. 2017;6(1):93-106. https://doi.org/10.18616/is.v6i1.2746

21. Higgins RD. Oxygen Saturation and Retinopathy of Prematurity. Clin Perinatol. 2019;46(3):593-9. https://doi.org/10.1016/j.clp.2019.05.008

22. Xavier MSLR, Santos TMSA. Ocorrência de retinopatia da prematuridade em recém-nascidos de muito baixo peso em maternidade de referência terciária no município de Fortaleza – CE. Rev Med UFC. 2019;59(4):7-13. https://doi.org/10.20513/2447-6595.2019v59n4p7-13

23. Tapia JL, Agost D, Alegria A, Standen J, Escobar M, Grandi C, et al. Bronchopulmonary dysplasia: incidence, risk factors and resource utilization in a population of South-American very low birth weight infants. J Pediatr. 2006;82(1):15-20. https://doi.org/10.1590/S0021-75572006000100005

24. Tarnow-Mordi W, Kirby A. Current Recommendations and Practice of Oxygen Therapy in Preterm Infants. Clin Perinatol. 2019;46(3):621-636. https://doi.org/10.1016/j.clp.2019.05.015