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ORIGINAL ARTICLE

High flow nasal cannula: is it a risk factor of bronchopulmonary dysplasia and retinopathy of premature?

Cánula nasal de alto flujo: ¿un factor de riesgo de displasia broncopulmonar y retinopatía del prematuro?

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What do we know about the subject matter of this study?

Randomized controlled studies have shown few differences in the evolution of preterm newborns when comparing the use of high-flow nasal cannula versus continuous positive airway pressure after withdrawal of invasive ventilation. However, observational studies have shown an increase in pathologies derived from greater exposure to oxygen with the incorporation of cannulae.

What does this study contribute to what is already known?

This analytical observational study shows a relevant association between increased bronchopulmonary dysplasia and retinopathy of prematurity related to the use of high-flow nasal cannula in a neonatal unit, without adequate protocol in the way it is used.

Abstract

Observational studies have described an increase in the duration of oxygen therapy, bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) in relation to the use of high-flow nasal cannula (HFNC, 2013-2016). **Objective:** to analyze changes in the evolution of very preterm newborns with the use of HFNC. **Patients and Method:** The incidence of neonatal pathologies between 2013 and 2021 was analyzed with a statistical process control. An analysis of cases (with HFNC, 2017-2021) and controls (without HFNC) was performed, 1:2, matched by weight and gestational age, comparing the main neonatal morbidities and respiratory support. Univariate analysis and logistic regression were performed with the variables associated with BPD and ROP. **Results:** 59 cases and 116 controls. The statistical process control revealed an increase in BPD and ROP over time, which coincides with the incorporation of the HFNC and with the increase in days of oxygen therapy. The case-control analysis showed an increase in respiratory support and oxygen therapy measures and greater severity at birth, according to the Apgar and Neocosur score, in the group with HFNC.

Keywords:
High-Flow Nasal Cannula; Very Low Birth Weight Preterm; Statistical Process Control; Retinopathy of Prematurity; Bronchopulmonary Dysplasia

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Logistic regression showed a significant association between the use of the HFNC and the risk of BPD and ROP. In addition, a longer duration of mechanical ventilation, lower birth weight, and more late sepsis were associated with BPD, and lower weight and gestational age at birth and longer duration of mechanical ventilation were associated with ROP. **Conclusions**: These findings require a quality improvement program to reduce BPD and ROP, seeking an adequate use of HFNC.

Introduction

In recent decades, the treatment of preterm respiratory distress syndrome has had advances that have contributed to a significant reduction in mortality[1,2]. The use of prenatal corticosteroids, continuous positive airway pressure (CPAP), different modalities of assisted ventilation, and intratracheal surfactant administration have improved survival, but with an important risk of chronic morbidity such as bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP)[3-5].

A few years ago, high-flow nasal cannula (HFNC) was incorporated into the withdrawal of assisted ventilation for premature newborns[6]. HFNC uses humidified and tempered air with flow rates greater than 1 L/min to deliver oxygen at a controlled concentration. Unlike CPAP, which delivers controlled airway pressure, HFNC does not allow this but facilitates nursing and parental care of the premature newborn, which has made it attractive for oxygen delivery at weaning from invasive ventilation as an alternative to CPAP[6,7].

Randomized controlled studies on weaning from assisted ventilation have shown similar success in avoiding reintubation and less nasal damage with the use of HFNC compared with CPAP[8-12]. Meta-analyses of these studies find no difference in the incidence of BPD but longer duration of oxygen therapy has been reported with the use of HFNC than with CPAP[13,14]. Several publications of retrospective observational studies have reported an increased incidence of BPD and ROP associated with the introduction of HFNC in respiratory support of premature newborns[15-18]. In the Neonatology Service of the *Complejo Asistencial Dr. Sótero del Río*, the use of HFNC was introduced at the beginning of 2017 as an alternative to CPAP for the withdrawal of assisted ventilation and as an intermediate stage between CPAP and low-flow cannula.

The objectives of this study were to analyze the respiratory evolution and its complications over time in very low birth weight (VLBW), very preterm newborns, , to compare cases treated with HFNC with historical controls without the use of HFNC, and to evaluate others factors associated with the incidence of BPD and ROP in this population.

Patients and Method

The general clinical evolution of VLBW preterm newborns born between January 2013 and July 2021 in the Neonatology Unit of the *Complejo Asistencial Dr. Sótero del Río*[19] was analyzed using statistical process control analysis. The analysis was performed by determining the incidence of the main morbidities of prematurity: late sepsis, necrotizing enterocolitis, oxygen requirements at 36 weeks, ROP, and pulmonary hemorrhage, with sequences of 20 VLBW preterm newborns discharged successively, as a period, with QI Macros Excel Add-in[20]. Given that the number of VLBW preterm patients admitted decreased markedly during the period analyzed, time intervals were not considered. In 2013, 63 cases were discharged, and in 2020, 39 VLBW preterm cases were discharged. The evolution was described with a p-chart of statistical analysis of process control[19,20]. These charts delineate a central line based on averages and add high and low limits, calculating the inherent variation of the data in standard deviations[20]. The software calculates the average as a fraction of 1 and draws lines corresponding to 1, 2, and 3 standard deviations, and records significant changes[20].

Deceased or transferred patients less than 30 days old were excluded.

Analysis of control cases

A case-control analysis was performed of VLBW preterm newborns under 32 weeks of gestational age, matched by weight and GA in a 1:2 ratio, between cases with and without the use of HFNC. The study group consisted of all VLBW newborns born between January 2017 and July 2021 who were treated with HFNC and discharged after 29 days of life. The control group were newborns with the same characteristics, born between January 2013 and December 2016, who never used HFNC, both groups were treated with CPAP and low-flow cannula according to medical indication. They were matched according to birth weight $\pm$ 100 g and gestational age $\pm$ 1 week. It was not possible to use a control group from the same period as the study group since it would have compared groups with very different characteristics at birth and in early clinical evolution.

The variables included were those registered in the NEOCOSUR Neonatal Network: prenatal history, immediate care, diagnoses, and therapies used. The Neocosur score, which predicts the risk of mortality and some morbidities, is also included[21,22].

BPD was considered to be the persistence of oxygen requirements greater than 21% at 36 weeks postgestational age. The retina was evaluated by specialized ophthalmologists using the RetCam from 28 to 33 days of age, and bi or weekly according to findings.

In the historical cases and controls, descriptive analysis was used with means, standard deviation, and median and interquartile range according to Bartlett's test and statistical analysis with analysis of variance (ANOVA), Kruskal-Wallis test, and Chi-square test. In addition, univariate analysis was performed, with determination of Odds ratio (OR) and 95% confidence interval of the variables associated with BPD and ROP and later logistic regression with the variables significantly associated in the univariate analysis. A $p < 0.05$ value was considered significant, and Epiinfo-7 and QI Macros Excel Add-in software were used.

The study was approved by the Ethics and Research Committee of the Chilean Eastern Metropolitan Health Service, on October 14, 2022, with waiver of consent for use of an anonymous clinical database.

Results

In the period studied (2013-2021), 563 VLBW preterm newborns were registered. 83 deceased cases and 8 cases transferred before 30 days were excluded. A total of 472 VLBW preterm newborns were included in process control analysis with QI Macros, which indicated a significant and sustained increase in the percentages of cases with oxygen at 28 days, home oxygen, age at discharge, discharge weight, oxygen at 36 weeks, and ROP since interval 14, which corresponded to the beginning of 2017. There were no differences between these periods in birth weight or gestational age (data not shown). Figures 1 and 2 show the control p-chart for BPD with a change from 23% to 51% and ROP from 14% to 36%, with a significant increase in both pathologies coinciding with period 14, already commented.

Analysis of control cases

Out of a population of 201 and 271, 59 study cases and 116 controls were analyzed, respectively, with a mean (SD) birth weight of 1022 g. (257) and 1007 g. (248), respectively, and mean (SD) gestational age of 27.5 (1.6) weeks in both groups. Table 1 describes the history and evolution of both groups. The case studies had significantly higher Neocosur score, lower Apgar at one minute, higher noninvasive ventilation, and use of surfactant in immediate care; higher use of surfactant (88.5 vs 66.4%), total days of respiratory support (days on CPAP + HFNC + invasive ventilation), days of oxygen, O2 at 28 days, O2 at 36 weeks, higher retinopathy, higher weight at 28 days, higher discharge weight, longer hospital stay, and higher gestational age at discharge. The rest of the variables analyzed did not have statistically significant differences, but in most of them, the frequency was higher in the study group.

In univariate analysis, the variables associated with BPD (table 2) were associated with lower Neocosur score, use of HFNC, gestational age less than 28 weeks, birth weight less than 1000 g, longer duration of mechanical ventilation, use of surfactant, having been intubated at birth, and late sepsis. The following were not significantly associated: prenatal corticosteroid use, sex, pulmonary hemorrhage, and ductus. The logistic regression analysis (table 2) highlighted a high OR for the use of HFNC, invasive ventilation of more than 6 days, and extremely low birth weight (< 1000 g) associated with BPD, the other variables not being significant.

The univariate analysis for ROP (table 3) showed a significant association with Neocosur score, duration of oxygen therapy greater than 28 days, use of HFNC, gestational age less than 28 weeks, birth weight less than 1000 g, mechanical ventilation longer than 6 days, and having been intubated at birth. Prenatal corticosteroid use, sex, late sepsis, surfactant use, pulmonary hemorrhage, and ductus were not significant. The second part of table 3 shows the logistic regression analysis, with a high OR for the use of HFNC, invasive ventilation of more than 6 days, gestational age less than 28 weeks, and birth weight less than 1000g.

Discussion

Monitoring the evolution of high-risk groups is fundamental in care improvement programs in critical care units[23,24]. In our unit, the increase in BPD and ROP in those born since 2017 proved marked in statistical process control. While different clinical practices or patient characteristics may modify the evolution of complications, here it concurs with the introduction of the use of HFNC in very preterm newborns. For this reason, we sought to analyze the factors associated with this increased risk through case-control analysis.

The analysis of a group matched by birth weight and gestational age before and after the use of HFNC shows a significant increase in the number of days of oxygen therapy, days of hospitalization, and a twofold increase in the incidence of BPD and a threefold increase in ROP between the two groups, observed in consecutive

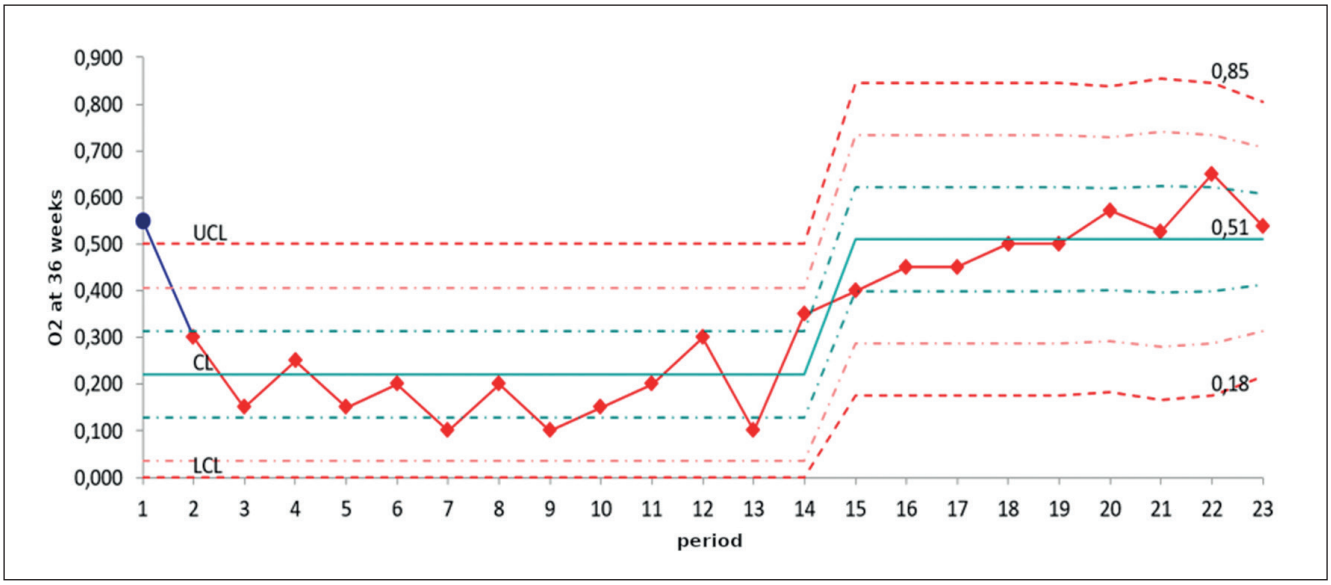

Figure 1. Oxygen use at 36 weeks for every 20 consecutively born VLBWs with p graph ofr statistical process control. A change is observed in period 14 to 15 from 23 to 51% in O2 use at 36 weeks.

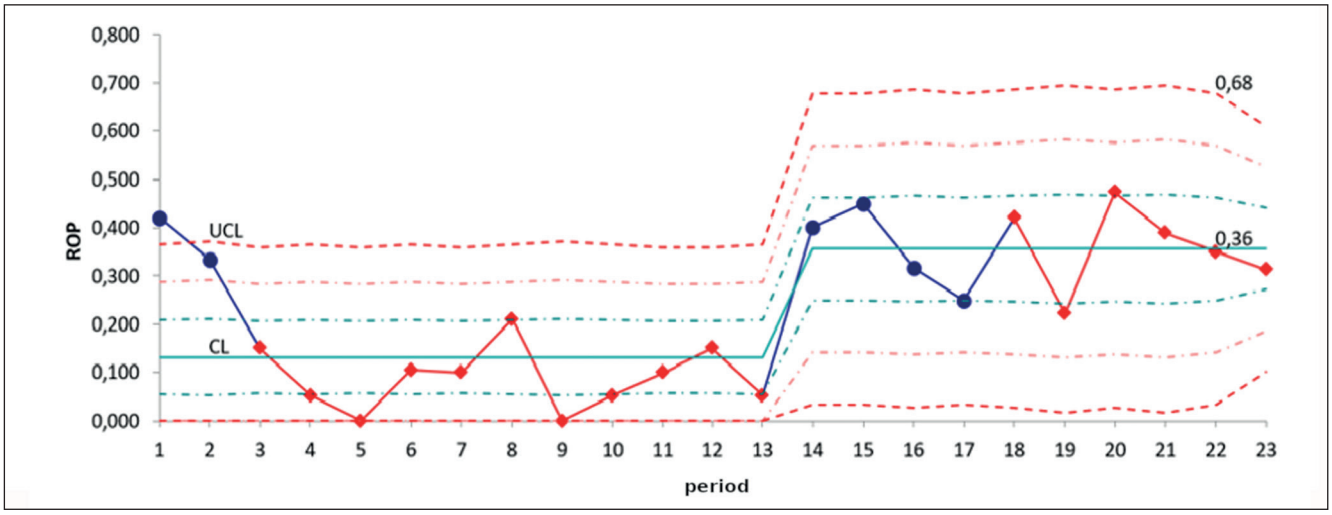

Figure 2. Retinopathy of Prematurity for every 20 consecutively born VLBWs with p-graph of statistical process control. A significant increase in the incidence of ROP is observed since period 14, which corresponds to the beginning of 2017. The blue color shows variations that require analysis.

periods. The Neocosur score, which measures mortality risk and is also applicable to some morbidities, is higher in the study group[21,22]. The score evaluates birth conditions and includes birth weight, gestational age, sex, prenatal corticosteroids, Apgar score at one minute, and life-threatening malformation. Of these, only the Apgar at one minute was lower in the study group, but the combination of the different factors may also play a role. The score measures a mark between 0 and 1 and the difference between 0.397 and 0.314 is statistically significant (p = 0.02), but it is not so different to influence so distinctly the difference in the incidence of BPD and ROP between the two groups, in fact, it does not remain significant in the logistic regression analysis.

The variables associated with BPD and ROP in the multiple regression are those usually described among the risk factors except HFNC, which has been reported in descriptive studies, but not in randomized controlled studies, although some do point to increased duration of oxygen therapy[13,14].

Given that the groups were successive, several factors of historical change may have influenced them. One of these is the saturation level to be maintained

Table 1. Analysis of perinatal history, therapies and evolution of the study group with HFNC and matched controls

	Study group	Grupo control	p
N	59	116	
Birth weight g mean (sd)	1.022 (257)	1.007 (248)	ns
Gestational age at birth mean (sd)	27.5 (1.6)	27.5 (1.6)	ns
Female sex %	44.9	35.6	ns
Prenatal corticosteroids %	91.5	92.4	ns
Neocosur score mean (sd)	0.397 (0.233)	0.314 (0.222)	0.02
Twins %	20.3	17.8	ns
Prenatal antibiotics %	42.4	47.5	ns
Membrane rupture days mean (sd)	16.8 (17.4)	11.1 (11.9)	ns
Caesarean section %	47.5	57.4	ns
Birth weight < p10 %	25.4	25.2	ns
Non-invasive ventilation in delivery room %	89.8	64.4	< 0.001
Intubation in delivery room %	62.7	52.5	ns
Surfactant in delivery room %	37.3	19.5	0.01
Adrenaline in delivery room diata %	1.5	2.7	ns
Apgar <3 at 1 minute %	40.7	24.6	0.028
Apgar <6 at 5 minute %	29.3	17.8	ns
Use of surfactant %	82.1	61.3	0.01
Surfactant dose number mean	1.74	1.63	ns
Invasive ventilation %	84.8	73.7	ns
Days of invasive ventilation median (IQ)	9 (4-28)	9 (3-25)	ns
Nasal CPAP %	100	94.9	ns
Nasal CPAP days mean (sd)	11.6 (8.7)	8.8 (9.2)	ns
Days total respiratory support median (IQ)	27 (15-37)	15 (4-38)	0.006
Days of oxigen mean (sd)	69.7 (38.2)	41.4 (42.1)	< 0.001
O2 at 28 days %	85	52	< 0.001
O2 at 36 weeks %	66	28	< 0.001
Alveolar rupture %	13.6	8.5	ns
Postnatal corticosteroids %	18.6	12.1	ns
Convulsions %	15.3	24	ns
Intracranial hemorrhage %	41.5	39	ns
Intracranial hemorrhage III and IV%	24.6	21.8	ns
Necrotizing enterocolitis %	18.6	16.1	ns
Late sepsis %	32.8	27.7	ns
Ductus %	68.6	55.9	ns
Number of antibiotic courses mean	2.0	2.1	ns
Days of parenteral nutrition mean (sd)	30.2 (21.3)	28 (21.9)	ns
100 ml/k/day enteral days median (IQ)	18 (12-28)	16 (12-25)	ns
Weight at 28 days mean (sd)	1.482 (322)	1.310 (310)	< 0.001
Weight at 36 weeks mean (sd)	2.240 (388)	2.119 (355)	0.0508
Retinopathy of prematurity %	45.8	14.7	< 0.001
Surgical retinopathy %	6.9	1.9	0.11
Weight at discharge mean (sd)	3.181 (708)	2.681 (617)	< 0.001
Hospitalization days mean (sd)	91.8 (32.4)	79 (30.2)	0.01
Gestagional age at discharge (sd)	40.6 (3.9)	38.7 (3.5)	0.0015

(sd): standart desviation. (IQ): Interquartile range. CPAP: continuous pressure in the airway.

Table 2. Univariate analysis and logistic regression associated with bronchopulmonary dysplasia

Variables	Univariate analysis			Logistic regression		
	OR	Intervalo de Confianza 95%	p	OR	Intervalo de Confianza 95%	p
Neocosur Score > 0,28	5.95	3.03-11.68	< 0.001			
Use of high flow cannula	5.02	2.56-9.84	< 0.001	11.67	4.24-32.13	**0.007**
Gestacional Weeks < 28	3.19	1.71-9.69	< 0.001			
Birth weight < 1000g	5.35	2.76-10.36	< 0.001	4.37	1.50-12.76	**0.001**
Invasive ventilation >6days	8.48	4.27-16.84	< 0.001	5.66	2.02- 15.86	**< 0.001**
Surfactant use	3.07	1.36-6.92	0.002			
Intubated at birth	3.21	1.69-6.11	< 0.001			
Late Sepsis	4.77	2.34-0.69	< 0.001	3.88	1.45-10.37	**0.007**

OR: Odds ratio

Tabla 3. Univariate analysis and logistic regression associated with retinopathy of prematurity

Variables	Univariate analysis			Logistic regression		
	OR	Intervalo de Confianza 95%	p	OR	Intervalo de Confianza 95%	p
O2 > 28 días	8.49	2.86-25.22	< 0.001			
Neocosur Score > 0.28	3.36	1.55-7.28	< 0.001			
Use of high flow cannula	4.9	2.35-10.25	< 0.001	11.22	3.87-32.6	**< 0.001**
Gestational age < 28 weeks	5.01	2.3-10.92	< 0.001	3.99	1.36-11.7	**0.022**
Birth weight < 1000g	4.49	2.03-9.94	< 0.001	3.71	1.19-11.64	**0.021**
Invasive Ventilation > 6 days	7.20	3.17-16.4	< 0.001	7.48	2.05-27.31	**0.004**
Intubated at birth	3.73	1.65-8.43	< 0.001			

RDP: retinopatía del prematuro, > 6 d: mayor de seis días, OR: Odds Ratio.

according to the Support and Boost II studies[25,26]. This is a factor that could influence, although published analyses show little change in the incidence of BPD and ROP with the higher oxygenation levels required and it is not confirmed that it is the change in saturation levels that has increased BPD because it has also been observed in centers where baseline saturation levels were not changed[27-30]. The incidence of BPD has been stable for many years but in the last decade, an increase is reported in many different publications, with no hypothesis[1,28]. The definition of BPD may change from one publication to another but is the same in the local comparison. We do not know if the change in saturation targets has influenced the prolongation of respiratory support in our unit. In the case group, less conventional ventilation and more high-frequency ventilation were used. It is not clear whether this change is due to greater severity, greater availability of the resource, or changes in clinical criteria for use. However, this difference should not have influenced the complications studied, given the lower lung damage expected with high-frequency ventilation[31].

Some publications that clearly point to increased duration of O2 delivery with HFNC use have compared extremely preterm or extremely low birth weight populations[15,16]. An observational study of a large population in the UK showed a higher risk of BPD, ROP requiring treatment, air leak, ductus with surgery, necrotizing enterocolitis, and late sepsis with HFNC than with CPAP[18].

Taha et al, suggest that the unregulated pressure of the high-flow cannula could produce overexpansion lung injury or atelectasis and thus contribute to the development of BPD[15].

The longer duration of oxygen therapy reported in some randomized studies and in most observational

studies alone constitutes a major risk factor for ROP[32].

Work-of-breathing physiology studies with HFNC and CPAP have shown greater respiratory pauses and higher O2 requirements with HFNC[33].

Other changes are observed in the data analyzed, such as the increase in surfactant administration in the immediate care room, meaning intubation, which may have influenced but are not significant in the regression analysis.

Randomized controlled studies provide the most evidence for clinical decisions, but in clinical practice, management may be very different, less protocolized, and orderly. The report of varied sites of increased BPD with the use of HFNC suggests that clinical practice may have been different from the protocols applied during investigations. Most randomized controlled studies of HFNC following assisted ventilation call for a flow decrease every 12 to 24 hours and are placed with oxygen levels below 30%, even 21%[8-12].

We observed that the patient on HFNC in the unit is considered a lower-risk patient than on CPAP, in fact, she/he is transferred to a lower level of care ward. In addition, patients remained many days with high flows, with no attempt to come down within 12 or 24 hours as was established in randomized studies comparing the use of CPAP or HFNC for withdrawal of assisted ventilation[6-8].

Incorporating the best evidence into clinical practices is no easy task. Establishing improvement in care requires complex collaborative work, measuring and evaluating outcomes in a continuous and timely manner to modify practices that have not led to improvement[23,24]. Unfortunately, it requires a good informatics system and the care team time to analyze, discuss, and incorporate new measures, which is not available in many neonatal units[23,24].

The strengths of this study are in showing the use of statistical process control to identify changes in the evolution of VLBW preterm patients and to search for factors that are associated with the observed changes.

Among the weaknesses is that the association of HFNC with the observed changes may be due to other unidentified variables or a change in the severity of the population. In addition, a late statistical process control analysis was performed because of the timing of tool acquisition.

Conclusion

In relation to the use of HFNC and other changes in respiratory management that increased the duration of oxygen therapy, a significant increase in pathology derived from oxidative damage such as BPD and ROP was observed. This situation requires an intervention to improve the quality of the respiratory management of the VLBW preterm newborn, identifying the type of patient who benefits from HFNC, and avoiding prolonging use by incorporating the indications of the protocol of the randomized studies that have not increased the risk of BPD and ROP. Eventually, a larger study could be proposed in the future, such as a clinical trial, aimed at clarifying the role of HFNC in neonatal management and the characteristics of the patients who would benefit from its use.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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