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ORIGINAL ARTICLE

Pulse Oximetry Values in Preterm infants at 34-36 weeks postmenstrual age

Valores de Oximetría de Pulso en Prematuros a las 34-36 semanas post-concepcional

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

Pulse oximetry (SpO2) is essential to guide oxygen therapy in preterm infants. Baseline values of SpO2 in preterm infants before discharge are limited. Most of the published studies do not detail the clinical condition and were performed without new-generation oximeters.

What does this study contribute to what is already known?

We report nocturnal SpO2 values in clinically stable preterm infants, without respiratory morbidity, using a new generation oximeter at 34-36 postconceptional weeks. These values can be used as a reference to guide pre-discharge oxygen therapy.

Abstract

Pulse oximetry (SpO_2) is essential for guiding oxygen therapy in preterm infants. Data on SpO_2 values before discharge are limited. **Objective***:* To establish SpO_2 values in asymptomatic premature infants at 34, 35, and 36 weeks of postmenstrual age (PMA). **Subjects and Method***:* Longitudinal, multicenter study carried out from May 2018 to May 2019 in three neonatal intensive care units in Santiago, Chile (altitude 579 m) which included premature infants born ≤ 32 weeks of gestational age, healthy, with clinical stability, and without respiratory morbidity at the moment of the study or until discharge. The following parameters were analyzed: mean accumulated SpO2 and SD, minimum SpO2 value, SpO2 time percentage < 90%, SpO2 time percentage < 80%, DI4, and DI80. Continuous overnight SpO_2 was obtained with Masimo Radical-7 or Rad-8 (USA), mean artifact-free-recording-time (AFRT) ≥ 6 hours. **Results:** 101 SpO_2 recordings were registered in 44, 33, and 24 studies at 34, 35,

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and 36 weeks of PMA, respectively, from 62 preterm infants, twenty-eight (45%) were male, median gestational age at birth 30 weeks (range 26-32), and median birth weight 1480 g (range 785-2700g). Oximetry variables were mean AFRT (± SD) 8.6 (± 1.5) hours; median mean SpO_2 96.9% (range 93.3-99.3%); median minimum SpO_2 74% (range 51-89%); median time of SpO_2 < 90% 2% (range 0-10.6%); median time of SpO_2 < 80% 0.1% (range 0-1.3%); median desaturation event ≥ 4% (DI4) within ≥ 10 seconds per hour sampled 15 (range 3.5-62.5); and median desaturation event <80% (DI80) 0.58 (range 0-10.8). We found no differences in SpO_2 values between the different PMA weeks. **Conclusions**: We described SpO_2 values in very preterm infants, asymptomatic at 34-36 PMA weeks. These values could be used as a reference for guiding oxygen therapy.

Introduction

Preterm birth has a global incidence of 15 million per year, with rates between 5% and 18%, depending on the country[1]. In Chile, they represent 8% of all live births[2]. According to the Neonatal Neocosur Network, extremely preterm infants (less than 32 weeks of gestational age or birth weight less than 1500 g) account for about 1 to 1.5% of all preterm births reported in Chile[3]. Most of these infants survive and are discharged with high morbidity rates, with bronchopulmonary dysplasia (BPD) as one of the most common conditions[1,3].

Long-term oxygen therapy is an important component of neonatal care, with BPD being its main indication[4]. However, saturation targets in this population are controversial, given the risk of hypoxemia and hyperoxemia at different periods[5,6].

Pulse oximetry (SpO2) is widely used in neonatal units. The latest generation of oximeters is safe and reliable for determining hypoxemia and has become an essential tool for guiding oxygen therapy. Some studies have reported SpO2 values in preterm infants[7-15], however, they were performed at different post-conceptional weeks and in different clinical conditions. In addition, not all studies were performed with an oximeter with signal extraction technology, so they might be less accurate.

The objective was to establish SpO2 values in clinically stable preterm infants, without respiratory morbidity at the time of evaluation and until discharge at 34, 35, and 36 postconceptional weeks, aiming for safe and evidence-based discharge.

Subjects and Method

Longitudinal study conducted in three neonatology units from the medical training centers *Hospital Clínico Red UC-Christus*, *Hospital Dr. Sótero de Río*, and *Hospital La Florida* of the *Pontificia Universidad Católica de Chile*, in Santiago, Chile (altitude 579 meters). Between May 2018 and May 2019, asymptomatic preterm infants born with ≤ 32 weeks of gestational age and/or < 1500 g were selected by convenience sampling. They were studied at 34, 35, and 36 postconceptional weeks only if they were breathing spontaneously, without any ventilatory support, and without the need for additional oxygen supply. Infants with the following significant neonatal morbidity were excluded: retinopathy of prematurity, periventricular leukomalacia, necrotizing enterocolitis, intraventricular hemorrhage, genetic disorders, pulmonary and/or airway malformation, BPD as defined by the 2001 Institute of Child Health and Human Development (ICHHD) guidelines[16], need for supplemental oxygen, congenital heart disease, and any other chronic or acute disease. We also excluded infants with current episodes of apnea of prematurity (AOP), defined as pauses in breathing of ≥ 20 seconds or a shorter pause accompanied by desaturation and/or bradycardia (< 100 bpm), cyanosis, or pallor. Caffeine use was not an exclusion criterion.

Demographic and clinical characteristics were obtained from the clinical records. Neonatal morbidity, nutritional status at the time of the study, and respiratory treatment (days of supplemental oxygen, days of caffeine use, and respiratory support [continuous positive airway pressure, mechanical ventilation, high-flow nasal cannula, and nasal cannula flow < 3L/min]) were recorded.

Measurements

Nocturnal SpO2 was recorded at least 6 hours continuously at 34, 35, and 36 postconceptional weeks. The equipment used was the Radical-7® or Radical-8® (Masimo Corporation, Irvine, CA, USA). These have signal extraction technology (SET®) and signal quality indicator (IQ®), which identify low confidence measurement conditions. The minimum recording interval allowed by this oximeter was programmed between 2-4 seconds. A Masimo LNCS-YI post-ductal neonatal sensor was placed on the newborn's foot or hand.

During the time of the study, neonates received routine neonatal care, including feeding. The nursing staff in charge recorded the events of desaturation and the schedule of care and feeding. Recordings were scheduled for three weeks postconceptional age if the newborn met the inclusion criteria and before discharge. Therefore, each subject could have undergone one and up to three measures.

Oximetry data analysis was performed by two members of the research team (IO, SC) using oximetry software (PROFOX Associates, Inc.). The valid recording time (VRT) was obtained by subtracting all periods with a low IQ signal from the total recording time. Preterm positions were not recorded. A significant desaturation event was defined as a drop of ≥ 4% (DI4). PROFOX software evaluated DI4 of ≥ 0 seconds and ≥ 10 seconds per hour sampled. An investigator (IO) also visually analyzed and recorded each desaturation event below 80% and calculated DI80 (number of desaturation events of less than 80% per hour sampled).

The following parameters were analyzed: mean cumulative SpO2 and SD, minimum SpO2 value, percentage of time of SpO2 < 90%, percentage of time of SpO2 < 80%, DI4, and DI80.

This study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine, *Pontificia Universidad Católica de Chile*, *Hospital Dr. Sótero del Río*, and *Hospital La Florida*. The parents of all participants signed and gave informed consent.

Statistics

Statistical analysis was performed with STATA 14.0. Continuous variables are shown as medians and ranges, and categorical variables as frequency and percentage. The Shapiro-Wilk test ruled out normal distribution of numerical variables, so comparisons between them were performed with the Mann-Whitney test, both for the total group and for each gestational age. Spearman's correlation test was used to associate numerical variables. To measure interobserver agreement for the variables mean SpO2, validity time, and SpO2 time below 90%, the Intraclass Correlation Coefficient (ICC) and its respective 95% CI were calculated.

Results

62 asymptomatic preterm infants entered the study, with 101 pulse oximetry studies performed, distributed in 44 at 34, 33 at 35, and 24 at 36 postconceptional weeks. Regarding the number of studies performed per newborn, 13 of them were studied at 34, 35, and 36 weeks, 12 patients twice, and 37 only once. Table 1 describes the clinical and demographic variables of the subjects included. Table 2 describes the clinical respiratory history before SpO2 measurement.

Regarding the use of oxygen, 11 preterm infants never received additional oxygen, and only one of them received it for 27 days. 18 studies were performed in preterm infants using caffeine. No clinically significant desaturation events were recorded during the feeding periods. We found no significant differences by sex for each of the variables studied, so the results are reported as a single group.

We found no significant differences when comparing the median mean SpO2 between neonates who had 2 or 3 studies with those in whom only 1 study was performed. The mean (± SD) VRT was 8.6 ± 1.5 hours. Table 3 shows the SpO2 variables obtained for the entire study group and separated by gestational age. We found no differences between the SpO2 values among the different gestational ages. Figures 1 and 2 show the frequency of mean SpO2 for the total studies and at each postconceptional week, respectively.

We analyzed the association between SpO2 values (mean saturation, SpO2 time < 90%, and SpO2 time < 80%) and clinical variables. We found no correlation between SpO2 values and caffeine use, anemia, having used surfactant, and history of apneas of prematurity ($p > 0.05$). In those preterm infants who had hyaline membrane disease (HMD), SpO2 time < 80% was slightly higher, with median (range) 0.1 (0-1.3) vs 0 (0-1.2) ($p < 0.05$). We found a weak positive correlation between days since caffeine suspension and days since oxygen suspension with higher SpO2 values, $r = +0.31$ ($p = 0.004$) and $r = +0.34$ ($p = 0.004$), respectively.

Agreement for interpretation between the two bronchopulmonary pediatricians reporting the studies was for VRT: 0.836 (0.586-0.935), for mean SpO2: 0.99 (0.998-0.999), and for SpO2 time < 90%: 0.995 (0.989-0.998).

Discussion

We obtained SpO2 values in a sample of 62 asymptomatic extreme preterm infants. Different studies have described SpO2 values in term newborns (17-20). In the case of preterm infants, the evidence is limited, and the main challenge is to recruit a healthy and representative sample of subjects.

Preterm infants have their own characteristics due to their condition, so they are not necessarily "healthy" and have comorbidities associated with prematurity. In this study, we performed SpO2 recordings in preterm infants in a stable clinical condition before discharge. Importantly, we did not include preterm infants younger than 26 weeks and/or weighing less than 785 grams, so this population, which has high respiratory morbidity, would not be well represented in our sample.

Most of the enrolled infants had HMD and required respiratory support during their first days of

Table 1. Newborn demographic and clinical characteristics

Total subjects, n	62
Female gender, n (%)	34 (55)
Gestational age (weeks), median (min-max)	30 (26-32)
Weight at birth (g), median (min-max)	1.480 (785-2.700)
Appropriate for gestational age, n (%)	46 (74)
Small for gestational age, n (%)	11 (18)
Large for gestational age, n (%)	5 (8)
Apgar score	
1 min, median (min-max)	8 (2-9)
5 min, median(min-max)	9 (6-10)
Antenatal corticosteroids, n (%)	57 (91)
Surfactant, n (%)	26 (42)

Table 2. Respiratory clinical characteristics before SpO_2 recordings

Total subjects, n	62
Newborn respiratory distress syndrome, n (%)	34 (55)
Transient tachipnea, n (%)	22 (35)
Respiratory support, n (%)	54 (87)
MV, n (%)	17 (27)
nCPAP, n (%)	53 (86)
HFNC, n (%)	6 (10)
NC, n (%)	18 (29)
Days of respiratory support (days), median (mín-máx)	3 (0-42)
MV	0 (0-8)
nCPAP	2 (0-23)
HFNC (days), median (mín-max)	0 (0-17)
NC (days), median (mín-max)	0 (0-16)
Supplemental oxygen, n (%)	50 (81)
Days of supplemental oxygen, median (mín-máx)	2 (0-27)
Apnea of prematurity, n (%)	43 (69)

MV, mechanical ventilation; nCPAP, Continuous Positive Airway Pressure; HFNC, High Flow Nasal Cannula; NC, Nasal Canula (< 3 L/min).

life. HMD has been reported in 30% of newborns younger than 30 weeks and up to 60% in those younger than 28 weeks[21,22]. Despite this, none of the preterm infants included in this study developed BPD or any other respiratory morbidity. We used the definition of BPD proposed by the ICHHD in 2001[16] which is the one most commonly used in the different neonatology services.

There were subjects who, for other reasons, including AOP, required nasal flow support for more days, without necessarily meeting the criteria for BPD. We tried to be accurate in showing the days of all types of respiratory support for each subject as there is a current trend to reclassify BPD based on this and not just oxygen dependency at day 28 of life[23-24]. Thus, we believe that the reader can be critical and interpret our values according to the reality of the preterm population under study.

With respect to AOP, in our cohort, 69% had a history of apneas before SpO2 measurement. It is important to consider that practically most newborns born before 32 weeks present AOP, with a reported incidence of up to 85% in newborns younger than 30 weeks[25]. All preterm infants included did not present apneas at least 7 days before SpO2 measurement. These characteristics make our cohort free of respiratory morbidity at the time of SpO2 measurements and the values obtained are representative of a population that could be considered healthy.

Caffeine use might be expected to affect SpO2 values. It has been proposed that methylxanthines increase minute volume, improve CO2 sensitivity, decrease hypoxic depression, enhance diaphragmatic activity, and decrease periodic breathing in preterm infants[26,27]. However, in our cohort, we studied preterm infants with and without caffeine use and found no difference in SpO2 values between the two groups. We

Table 3. Oximetry variables

	Mean SpO_2 median (range)	Minimum SpO_2 median (range)	Total time of SpO_2 < 90%) median (range)	Total time of SpO_2 < 80% median (range)	DI80 median (range)	DI4^ median (range)	DI4^^ mediana (rango)
Total recordings (n = 101)	96.9 (93.3-99.3)	74 (51-89)	2 (0-10.6)	0.1 (0-1.3)	0.58 (0-10.8)	45.2 (5.2-115)	15 (3.5-62.5)
34 weeks PMA (n = 44)	96.9 (93.6 - 98.9)	76 (62 - 88)	1.5 (0 - 10.6)	0.1 (0 - 1.3)	0.6 (0 - 10.5)	45.3 (6.2-107.9)	14.9 (3.5-42)
35 weeks PMA (n = 33)	96.5 (94.1 - 98.9)	72 (51 - 84)	2.7 (0.3 - 10.2)	0.1 (0 - 1.3)	1.46 (0 - 7)	45.2 (14.4-114.6)	16.3 (5.2-28)
36 weeks PMA (n = 24)	97.3 (93.3 - 99.3)	75 (61 - 89)	1.6 (0 - 9.3)	0 (0 - 1.1)	0.36 (0 -10)	46.1 (5.1-115.7)	15.5 (4.4-62.5)
	*	*	*	*	*	*	*

SpO_2: pulse oximetry; DI4^, decrease of saturation by 4 or more, events ≥ 0 sec per sampled hour; DI4^^, decrease of saturation by 4 or more, events ≥ 10 sec per sampled hour ; DI80: desaturation event index under 80%; *p > 0.05

found a weak positive correlation between days since caffeine discontinuation and days since oxygen discontinuation with higher SpO2 values. We believe that this could be because preterm infants with fewer days of oxygen and/or caffeine use have a higher maturity and therefore present a better SpO2 profile, which could be due in part to the absence of AOP.

Hypoxemia during a period of apnea in preterm infants is related to the immaturity of the respiratory system. Preterm infants have lower exhaled lung volume, immaturity in the coordination of swallowing mechanisms, immaturity of laryngeal chemoreflexes, greater diaphragmatic fatigue during feeding, and greater susceptibility to upper airway obstruction. In addition, they present an inappropriate response to hypoxia and hypercarbia[28].

AOPs cease spontaneously at 36 to 43 postconceptional weeks. Observational studies have shown that once they resolve, SpO2 values increase[7], so it is expected that once apneas are resolved there will be no difference between SpO2 values.

We did not find differences between SpO2 values according to history of anemia or surfactant use. This finding is to be expected, considering that anemia influences oxygen content, but not hemoglobin saturation. Regarding the use of surfactant, its early use has been shown to reduce the incidence of HMD and mortality. However, it has not been shown to reduce long-term respiratory morbidity in premature infants[29].

As we have previously mentioned, some studies have reported normal SpO2 values in preterm infants. These studies have been performed with few subjects, not necessarily before discharge, and with different technologies to measure SpO2. As in our study, Rath et al.[14] found 3% of the time SpO2 < 90% using the Radical-7 oximeter. This study was done at 37 postconceptional weeks in 15 preterm infants born < 28 weeks. Rhein et al.[10], in 52 preterm infants born < 32 weeks, also with Radical-7 oximeter, found a median (range) mean saturation of 99% 95-100% and a SpO2 < 90% time of 3.2%. Other studies are using other types of pulse oximeters that report different SpO2 values[12,13,15]. These differences between studies may be explained by the different technologies used to perform SpO2 measurements and the different averaging times used.

There is a wide range of pulse oximeters performance. Patient movement is the most frequent cause of measurement error. We use Masimo equipment with SET® technology for our measurements which has demonstrated greater accuracy during movement and hypoperfusion in newborns[30]. In addition, we programmed short averaging times (2-4 seconds), which increases the detection of short desaturation events[31].

Different studies have proposed that DI3 and DI4 intermittent desaturation events may be physiological

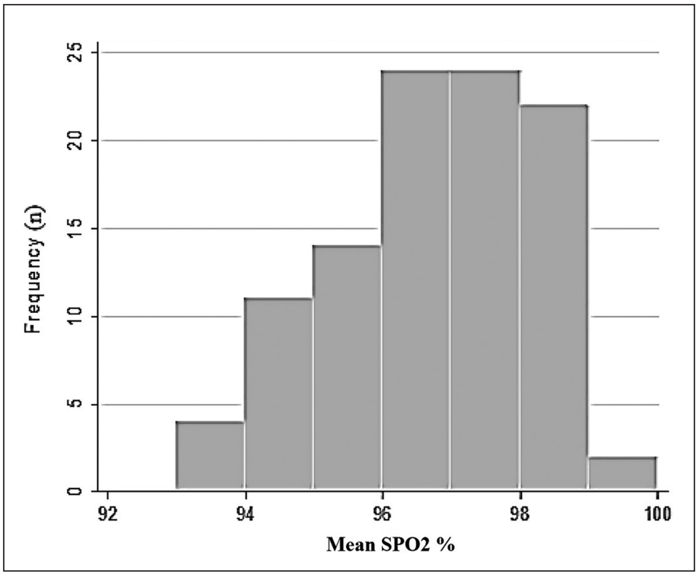

Figure 1. Mean oxygen saturation (mean SpO2 %) for total recordings (n = 101).

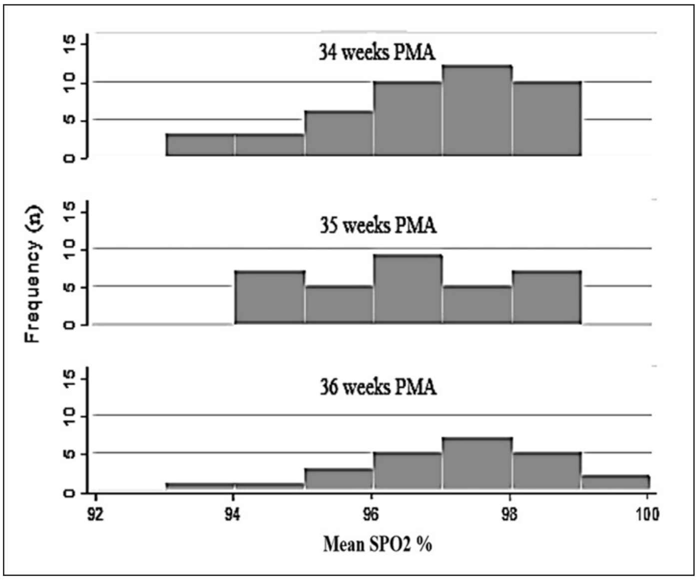

Figure 2. Mean oxygen saturation (mean SpO2 %) at 34, 35 and 36 weeks PMA.

before 12 months of life and are greatest during the newborn period[10,17-18,20,32-33]. Evans et al.[20], in a cohort of term infants, describe a decrease in average DI4 from 16 events per hour at 1 month of life to 8 events per hour at 3-4 months of life, but with similar SpO2 averages between both ages. Regarding DI4, our values are similar to those found by Rhein et al.[10] if we consider desaturation events ≥ 10 seconds per hour sampled. However, if we consider any desaturation event ≥ 0 seconds per hour sampled, our values are higher. The clinical significance of this difference requires further study.

Regarding desaturations < 80%, Poets et al.[7] in the follow-up of 160 preterm infants born < 32 weeks, found a negative correlation between baseline SpO2 and the frequency of desaturation events < 80%. The authors observed that, at an older age, basal saturation increases, and desaturation events decrease.

In our cohort, we found a median (range) DI80 of 0.58 (0-10.8) for the total studies, with no differences between the different postconceptional weeks evaluated. Preterm infants may have a physiologically higher DI80 value than term infants which appears to decrease as respiratory control matures[7]. In a cohort of 37 term infants, Brockman et al.[18] analyzed polygraph values between the age of 1 and 3 months, concluding that higher DI3 may be normal at this age, with few or no episodes of DI80. The authors describe a median (range) DI80 of 0 (0-0.9) at 1 month of age. We agree with the authors that oximetry and sleep studies should consider these variables for interpretation. The use of parameters from older children or adults could overdiagnose hypoxemia or desaturation events, resulting in an inadequate indication for oxygen therapy.

In the group of preterm infants with HMD, the time to SpO2 < 80% was slightly longer. This finding could reflect the immaturity of the respiratory system, characterized by low surfactant production[22]. However, the clinical differences of this finding are debatable and require further study.

The strengths of our study are that the preterm infants studied came from different neonatology units, were healthy at the time of SpO2 measurement, and we used new-generation oximeters with high accuracy. One of the limitations is the probable bias that could occur due to information obtained from the same subject on 2 to 3 occasions. However, we found no differences between the values obtained at the different gestational ages studied. Another limitation is that we did not follow up on the preterm infants after discharge, so we do not know the long-term implications of our findings.

Conclusions

We defined SpO2 values in asymptomatic extreme preterm infants at 34, 35, and 36 postconceptional weeks. The indication for supplemental oxygen is usually based on studies performed in term newborns which is not always appropriate. Mean SpO2 is similar at different gestational ages, but desaturation events decrease with age. We believe that our results constitute a representative sample of SpO2 values that could be used as a reference to guide home oxygen therapy before discharge.

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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