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Observation of mortality in extremely preterm newborns related to conditions of low or high oxygen supplementation beyond the target saturation range: A literature review

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Jaqueline Fernanda Felix Bertoncelo
Degree in Physiotherapy, HU-FMJ
E-mail: jaqueline.bertoncelo@outlook.com

Alex Oliveira
Doctor of Health Sciences, Jundiaí Faculty of Medicine
E-mail: ftalexoliveira@gmail.com

ABSTRACT
Prematurity is defined as a birth that occurs before 37 gestational weeks, and is often associated with the need for oxygen supplementation, however the saturation target of this population is debatable and is still widely debated, and some negatives were pointed out. This study aims to systematically review the available literature and evaluate the mortality associated with a target range of low and high saturation in extremely premature newborns, and the associated secondary ones as their respective pre-established saturation ranges. A review was performed based on eligible studies found through searches in the Pubmed and Scielo databases. Some negatives were pointed out, such as retinopathy of prematurity, cerebral palsy, neurodevelopmental impairment, septicemia, necrotizing enterocolitis, persistent increase in systolic blood pressure in adulthood, long-term bronchial hyperreactivity and death. Mortality is often related to lower saturation levels, making it relevant to understand this association to better define a target saturation range that minimizes related complications in this population.

Keywords: Oxigen saturation, Premature Infant, Mortality.

1 INTRODUCTION

Prematurity is defined as birth that occurs before 37 gestational weeks, and is subdivided into: moderate prematurity when birth occurs between 26 and 32 weeks of gestation, very premature born between 28 and 31 gestational weeks, and extremely premature those born below 28 weeks. The national health agency (ANS) reports that 11.7% of births in Brazil take place before the 37th gestational week, making the country occupy the 10th place in the world ranking of prematurity.

In this population, among other conditions, we are faced with immaturity of the respiratory system, often resulting in episodes of apnea, irregular breathing pattern, saturation drops, intermittent hypoxemia, among others, and oxygen supplementation is widely used. [1-3 years]

However, the saturation target for extremely preterm newborns is still uncertain and has been debated, since hyperoxemia and hypoxemia carry significant risks, and specifically in this population some negative outcomes have been pointed out, such as retinopathy of prematurity, cerebral palsy, neurodevelopmental impairment, septicemia, necrotizing enterocolitis, persistent systolic blood pressure elevation in adulthood, and mortality [1-7,]

It is not only inadvertent oxygen therapy that is related to high oxidative stress in premature newborns, there are other factors contributing to this condition such as being exposed to inflammation, frequent blood transfusions, parenteral nutrition and having a poorly developed defense system in relation to oxidative stress, so it is possible to understand the multifactoriness of this condition, however, having adequate control of O2 supplementation is one of the fundamental approaches to reduce oxidative stress.[5]

Pulse oximetry is the most commonly used and appropriate tool to monitor bedside O2 saturation, and it is possible to guide the titration of supplemental oxygen to provide it adequately to the patient.[3-6 years]

In view of the above, this study aims to systematically review the available literature and evaluate whether mortality is associated with a deviation from the target saturation range, low and/or high in extremely preterm newborns, as well as the secondary outcomes associated with their respective pre-established saturation ranges.

2 METHOD

It refers to a literature review conducted with the purpose of evaluating, as a primary outcome, the mortality rate associated with high and low saturation targets in extremely preterm newborns.

The descriptors were consulted in the health science descriptors (DECs), and the following descriptors were found: "oxygen saturation", "premature newborn", "mortality", "Oxygen saturation", "infant, premature" and "mortality"

Subsequently, the Pubmed and Scielo databases were searched. The search in pubmed was done with the following combination "Oxygen saturation and infant premature ", initially resulting in 1480 articles, of which after reading the titles and abstracts, 21 were chosen to read in full. With the application of filters (full text, clinical trial, meta-analysis, controlled and randomized test, being published in the last 5 years) to this combination of descriptors, this number reduced to 109 results. After reading the titles, 6 papers remained, and the abstracts were read and 3 were chosen for the complete reading. Performing the same associations of descriptors with the publication date extended to the last 10 years, 16 results were found and 4 articles were selected for full reading. Another combination performed in this database was "Oxygen saturation and infant premature and mortality", applied the same filters mentioned above, with 8 results, after reading the titles and abstracts, an article was selected for complete reading.

The search in the Scielo Database was carried out with the descriptor "premature newborn", with 477 results, after reading the titles, 3 articles were selected for reading in full. Thus, 5 articles were used for this review.

3 RESULTS

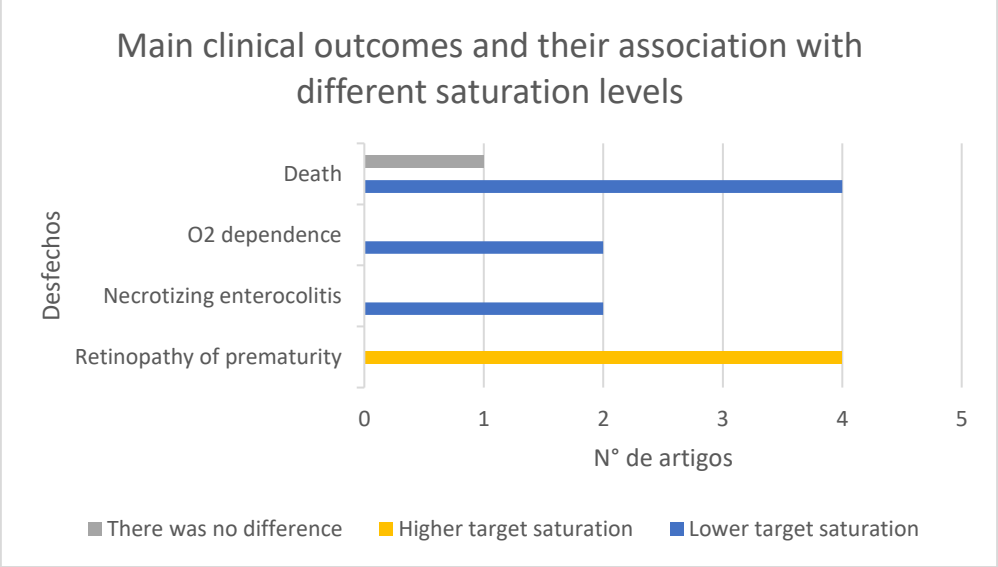
Table 1: Association of mortality to target saturation range

Authors/year	Type of study	Specimen characteristics	Target Saturation	Significant results
Oren et al [7] (2020)	Cohort	387 Neonates aged 24-27 weeks and 6 days were included in the analysis, randomized to lower and upper saturation target	Inferior: 85-89% Superior: 91-95%	The mortality rate was similar between the groups.
BOOST II [13] (2013)	Randomized controlled clinical trial	2448 recruited, born before 28 weeks of gestational age	Inferior: 85-89% Superior: 91-95%	Mortality was higher in the group with lower target saturation than in a group with a higher target.
Schmidt et al [14] (2013)	Randomized double-blind study	1201 babies from 23 weeks to 27 weeks and 6 days	Inferior: 85-89% Superior: 91-95%	51.6% of infants in the lower target range died or had disability, compared to 49.7% of the group with target saturation between 91 and 95%
[2] BOOST-II (2016)	Randomized clinical trial	It involved 15 Australian and 34 UK centres	Inferior: 85-89% Superior: 91-95%	Disability rate and death were more frequent in the group with lower saturation target
Walsh et al [15] 2016	Randomized clinical trial	1316 babies included, divided into AGA and SGA groups.	Inferior: 85-89% Superior: 91-95%	237 of the 1316 children included in the study died, 37 of whom were SGA and 200 AGA.

Legend: GA - gestational age; Fio2 - Fraction of inspired oxygen; SGA – small for gestational age; AGA – suitable for gestational age

Source: table developed by the authors themselves

Graph 1 :P main clinical outcomes and their association with different levels of saturation



Caption: O2 dependence: need for supplemental oxygen after 36 weeks; Lower target saturation: 85% to 89%, higher target saturation: 91% to 95%.

Source: Graph developed by the authors themselves

The main negative outcomes are associated with lower saturation targets, and only retinopathy of prematurity is often related to higher saturation levels. Other outcomes found did not show statistically relevant differences between the saturation targets observed, such as intraventricular hemorrhage, patent ductus arteriosus, hearing loss, blindness, cognitive delay, among others.

4 DISCUSSION

Extreme prematurity is defined as birth occurring between 22 and 28 weeks of gestational age, several conditions are related to the occurrence of prematurity, such as genetic, environmental and pregnancy-related factors.[10]

Prematurity is considered an important cause of neonatal death, and this population has an incomplete fetal development, which brings greater risks of morbidity and mortality, in addition to other factors that develop as a result of these conditions, such as greater manipulation, need for invasive procedures, prolonged stay in neonatal units, also considering the fact that they are more subject to infections. [8,9,10] These situations can lead to neurological, ophthalmological, or pulmonary developmental sequelae.[10] With regard to the respiratory system, due to this immaturity and sequelae, oxygen supplementation is widely used and necessary, but it is still a challenge as to the ideal saturation target for this specific population.

Hypoxia can be defined as the insufficient supply of O2 to meet the demands of the tissues, as opposed to hyperoxia, which corresponds to the excessive supply of O2 in relation to the demand.[11]

In an attempt to avoid periods of hypoxia in patients, it is possible that professionals expose patients to hyperoxemia, being considered an iatrogenic condition, which the body has no mechanisms to deal with, since this does not occur in nature.[11.12]

In the 1950s, studies showed that the supply of O2 without restriction was associated with higher rates of retinopathy of prematurity. On the other hand, lower supply was related to higher mortality. Several studies point to retinopathy as a finding associated with lower target saturation, and its treatment is usually efficient, but it may be associated with the cause of other ocular abnormalities that interfere with the quality of survival. Necrotizing enterocolitis is a consistent finding of the lower target saturation group, requiring surgical procedure and possibly associated with death.[13]

Oren et al [7] (2020) in their study that consisted of analyzing data in a cohort of 387 school-age children, analyzing oxygen saturation and blood pressure, were randomly separated into 2 groups, one group with higher target saturation and the other with higher saturation target, 85-89% and 91-95% respectively, The group with higher saturation target had more reports of retinopathy of prematurity and bronchopulmonary dysplasia. The proportion of mortality did not differ in the two groups, with a survival rate of 94-96%.

Another study shows similar results, where, through a randomized double-blind study conducted in 25 hospitals, the primary outcome observed was death before 18 months (corrected age) or survival with cognitive or language delay, bilateral hearing loss, and severe motor impairment. Among the 1201 babies analyzed, the previously established lowest and highest saturations did not differ significantly in the rate of death or disability, presenting in their results a mortality rate of 16.6% in the lower target group and 15.3% in the upper group. [14th]

This is different from the sample of the BOOST II study (2013), which consisted of evaluating 2448 infants (United Kingdom, Australia and New Zealand) randomized into a group with a pre-established upper target saturation between 91 and 95% and lower saturation between 85 and 89%. In the results presented, there was a difference in the mortality rate between the groups, with the lower group being associated with 23.1% mortality before hospital discharge, compared to 15.9% in the group with higher target saturation. The author also points out that 14 infants who had a saturation target between 85-89% needed to readjust the saturation target to an upper limit in order to avoid death. In this study, retinopathy was more associated with higher saturation (13.5%). Cases of necrotizing enterocolitis that required surgical intervention or were the cause of death were more associated with the lower target group, corresponding to 10.4% of the population. As soon as the analysis of the study showed a greater association of death with a lower target range of saturation, the study was terminated early

In the study carried out in 15 Australian and 34 UK centres, as well as in other studies already mentioned, the oximeters were modified so that the true reading would not be identified by observers, and a saturation of 3 percentage points more and less was displayed in the lower and upper target saturation group, respectively. In the Australian sample, 2454 patients were assessed for eligibility, 2228 of which were eligible and of these 1135 underwent randomization, of these 568 participated in the lower target and 567 in an upper target group. In the UK, 973 infants were enrolled, randomly separated into 366 for the lower target group and 357 for the upper target group. The authors report that the baseline characteristics of the population were similar between the groups. In both trials, with or without reviewed oximeters, disability rate and death were more frequent in the group with lower saturation target. The main causes of death reported included necrotizing enterocolitis, sepsis, intraventricular hemorrhage, and chronic lung disease.[2]

Walsh et al [15] (2016) make an association not only with target saturation levels, but also with the relationship between weight and gestational age and its possible correlation with mortality in preterm newborns. 1316 patients were included, of which 1220 were infants suitable for gestational age (AGA) and 96 SGA (small for gestational age), 237 children died, 37 SGA and 200 AGA infants.

The SGA group had a higher mortality rate associated with lower target saturation, corresponding to 56.1%, compared to 25.5% mortality in the upper target group. AGA babies, even

when exposed to a lower saturation target, did not present the same mortality, which is not usually differentiated in the analyses of the previously mentioned studies. The author suggests that infants considered small for gestational age may present hypoxia in the intrauterine period, reflecting on their respiratory control or affecting pulmonary vascular resistance, generating increased vulnerability to lower saturation targets. [15th]

Another finding is pointed out in the study by Di Fiore et al [1] (2019), which consists of data collection from a cohort in Ohio, consisting of 137 premature newborns with gestational age between 24 and 28 weeks, the primary outcome sought in this study aimed to observe the use of asthma medication in the first two years of life, Bronchopulmonary dysplasia (BPD) was also associated with the use of medications, and intermittent hypoxemia in the first 3 to 7 days may be associated with long-term respiratory morbidity, suggesting that these episodes of hypoxemia associated with oxygen supplementation predispose to long-term hyperreactivity.

Between 2005 and 2007, the collaboration called NeOprom (Neonatal oxigen prospective goal –analysis) included 5 randomized studies comparing lower and upper target saturation in relation to its effects on premature babies. In conclusion, in agreement with other studies cited here, low SPO2 may be associated with higher mortality and necrotizing enterocolitis and higher saturation related to retinopathy of prematurity.[16]

The lower and upper target saturation range ranged from 85-89% and 91-95%, respectively, and intermediate ranges were not addressed in the reviewed studies, compared to a higher target range, and currently evidence suggests that saturation between 91-95% is safer and less associated with death in extremely preterm newborns.[12th]

In view of the above, further research is suggested to elucidate the subject, taking into account the different baseline characteristics of extremely preterm infants and other saturation ranges, since all studies are based on the same saturation range.

5 CONCLUSION

According to the literature review, mortality in preterm newborns has a greater relationship with a lower saturation target, although in some studies the difference is not statistically significant.

An inadequate oxygen supply in this population can result in unfavorable outcomes, such as necrotizing enterocolitis, aiming at a lower saturation target, and with a higher saturation target, the occurrence of retinopathy of prematurity is more frequently found, such as cerebral palsy, neurodevelopmental impairment, septicemia, persistent systolic blood pressure elevation in adulthood, which are not significantly associated with a range of saturation-specific.

New studies with practical perspectives may bring more information on this topic, especially in this population of newborn patients who, due to small adjustments, may not suffer later from permanent damage.

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