REGION KRONOBERG

Supplemental oxygen to infants

- Compliance to target range at NICU in Växjö?

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1. Introduction

Why oxygen is needed?

Oxygen therapy is a cornerstone in neonatal intensive care both for the ill term and the prematurely born infant(1). For the ill term infant conditions like pneumonia, sepsis, different types of neonatal respiratory disorders or asphyxia often demands oxygen therapy. The preterm infant almost always needs supplemental oxygen not only because of the above-mentioned conditions, that also can occur to the premature infant, but mainly because of their immature lungs. Preterm infants have underdeveloped lungs. Between week 22 and 40 of development a vital differentiation occurs in the lung parenchyma of the fetus, crucial to make gas exchange sufficient. Through week 22-24 of gestation rapid development begins of the fetus's pulmonary vasculature, respiratory bronchi and alveolar ducts. During this time the respiratory epithelium differentiates into type I and type II pneumocytes. Type II pneumocytes produce and store surfactant. During week 24-40 there will be a further differentiation involving proliferation of the pulmonary vascular bed, a decrease in the volume of mesenchyme, fusion of the gas-exchange epithelium to the pulmonary capillary epithelium, and a creation of new alveolar ducts and alveoli. A child born during this important time of lung development will have insufficient gas exchange and will need respiratory support (2). A common condition caused by lack of surfactant due to immaturity is respiratory distress syndrome, RDS. The premature infant also has an immature breathing pattern, with central apnoea, often associated with bradycardia and/or desaturation. RDS and apnoea are conditions that partly are treated with supplemental oxygen (3).

Why oxygen isn't harmless?

It is well understood that both too little oxygen (hypoxia) and too much oxygen (hyperoxia) are harmful to infants (2). Hypoxia might cause severe brain injury, cerebral palsy or even death (4). Hyperoxia might not cause an instant effect like hypoxia, but it can still cause severe complications. Excessively high levels of oxygen cause metabolic intracellular changes and production of reactive oxygen species (5). Preterm infants are less well adapted to handle oxidative stress because they do not have an adequate endogenous production of anti-oxidants. They often have a nutritional problem and are therefore less likely to receive anti-oxidants through their feeds. An additional contributing factor is different conditions or diseases that will make infants more vulnerable to oxidative stress and the same goes for the ill term infants (2). Organs such as eyes, gut and lungs can be extra sensitive for oxidative stress.

Periods with hyperoxia may cause retinopathy of prematurity (ROP) and fluctuations between hypoxia and hyperoxia may contribute to development of ROP, bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC) (2, 6). The main risk factors for developing ROP are premature birth and supplemental oxygen therapy, two things that often come together. Severe cases of ROP can cause detachment of the retina, which might cause blindness (2, 7). Infants born prematurely do not have fully vascularized eyes at birth. As the infant matures the non-vascularized areas of the eye become metabolically active. This in turn can lead to tissue hypoxia. These periods of hypoxia stimulate excessive production of vascular endothelial growth factor (VEGF) which can lead to an over proliferation of retinal blood vessels. Controlling the amount of supplemental oxygen administered to premature infants might minimize repeated episodes of hypoxia/hyperoxia and could potentially reduce the development of ROP (7).

The causes of NEC are not fully understood but contributing factors are ischemia, oxidative stress and reperfusion injuries as result of hypoxia and hyperoxia. NEC is potential deadly with a mortality rate of 17% in all cases, 20% in very low birth weight infants (VLBW) and 40-50% in extremely low birth weight infants (ELBW) (6).

BPD can be viewed as a chronic phase of RDS. RDS needs to be treated with respiratory support, however mechanical ventilation and oxygen therapy might contribute to the development of BPD by inhibit lung healing (2, 8).

How to define hypoxia and hyperoxia?

Everyone agrees that both hypoxia and hyperoxia should be avoided, but the question of the ideal target range for SpO2 is still debated. During the years several studies have been made trying to better clarify the connection between partial pressure of arterial oxygen tension (PaO2), SpO2 and long-term outcomes. One study stated that a PaO2 of 40mmHg will meet the tissues need given adequate cardiac output, blood flow, Hb concentrations and cellular conditions in an infant. Hyperoxia was in this study defined as PaO2 above 80 mmHg (4). The same study and several more then tried to find the equivalent levels for SpO2 but only vague recommendations could be made (4, 9, 10). For example Quine et al. (10) showed that oxygen saturations within the broad range of 85-95% largely exclude hyperoxia in preterm infants less than 29 weeks gestation. In summery the difficulty lies in converting PaO2 values into SpO2 values because so many factors affect the oxyhemoglobin dissociation curve.

The largest recently published study Neonatal Oxygenation Prospective Meta-analysis (NeOProm) (11) looked in to SpO2-levels and long-term outcome. NeOProm includes five randomised control trials (SUPPORT, BOOST 2 Australia, BOOST 2 New Zealand, BOOST 2 UK and COT) with almost 5000 premature infants receiving supplemental oxygen. They were randomly assigned to

either target range 85%-89% or 91-95%. Primary outcome of death or disability at a corrected age of 18-24 months did not differ significantly between the groups. Looking at secondary outcome NeOProm found that assignment to the higher target range reduced the risk of death and severe NEC but increased the risk of severe ROP looking at relative risks. Both the Swedish Socialstyrelsen and the European Consensus Guidelines on the Management of Respiratory Distress Syndrome refers to NeOProm when recommending target range of 91-95% and 90-94% respectively (12, 13).

A neonatal child is known for big fluctuations in saturation, that makes it part of the problem finding the optimal target range. If we do not know the proportion of time spent within a predefined target range for saturation it will be difficult to draw conclusions. This study aims to look at time spent within target range.

How oxygen is administered?

You can support infants' respiration through non-invasive ventilation if the infants are breathing spontaneously but still do not have adequate oxygen levels or through mechanical ventilation via endotracheal tube when infants' respiratory drive is absent or inadequate. For a spontaneously breathing infant first of choice is nasal continuous positive airway pressure (CPAP). With CPAP a fixed amount of positive airway pressure is present throughout the whole respiratory cycle delivered by mask or prongs. Other methods in use are nasal intermittent positive pressure ventilation (NIPPV) and high flow nasal canula (HFNC). NIPPV delivers different pressure during the respiratory cycle and HFNC comes with heated and moistened air. Oxygen can be administered by all methods (12). Indications for prescribing supplemental oxygen for an infant are low PaO2, clinical signs of respiratory distress, central cyanosis, apnoea or low SpO2(2).

How oxygen therapy is monitored?

Infants admitted to a Neonatal Intensive Care Unit (NICU) are closely monitored by bedside nurses. In response to changes in oxygen levels the nurses are responsible to manually adjust the fraction of inspired oxygen (FiO2). In infants oxygen can be measured directly in arterial blood (PaO2) or transcutaneously (SpO2). There are advantages and disadvantages with each method. Most accurate readings are given when measuring PaO2 by taking arterial blood gases, though this is not always appropriate in neonatal care. Considering the fact that infants have approximately 90 ml blood per kilo and the smallest ones weigh just above 500 grams, a continuous sampling of blood would make the infants anemic (14). Only blood samples from a central arterial line, like an umbilicus arterial catheter would give accurate values for PaO2 and all infants do not have an

arterial line. Instead SpO2 is measured with a pulse oximeter. The pulse oximeter is non-invasive and allows continuous measurements to be made. A pulse oximeter measure oxygen saturation by the physical property that blood changes colour as haemoglobin absorbs varying amounts of light depending on the saturation. Two wavelengths, red (660 nm) and near infrared light (940 nm), are used to distinguish between oxygenated and deoxygenated blood. Passing light through a capillary bed measures the changes in light absorption during the pulsatile cycle (15-17).

How do we know it's hard to keep infants within target?

As briefly mentioned earlier the monitoring of saturation can be problematic, especially for ill premature infants whose oxygenation frequently fluctuate both because of immaturity in breathing and of underlying conditions. This is illustrated in several studies looking at premature infants receiving supplemental oxygen. These studies have different study designs, but similar target ranges and the results show a wide variety of time spent within target reaching from only 16% to 59% (18-21) . Others have looked into improving manual oxygen titration by training and guidelines implementation with good results showing increased time within target and less frequent episodes with hyperoxia (22, 23). Recent years automatic delivery of oxygen with closed loop systems for FiO2 has become available and some NICUs have implemented it in their daily care. A review by Dani et al(24) looked at 15 studies all with different study designs. All studies reported that automated devices were significantly more effective than traditional manual control in maintaining SpO2 within selected target range and in preventing episodes with hyperoxia, while they seem to be less effective in preventing hypoxia. No study looked at long-term outcome. Many studies are ongoing investigating the best algorithm for closed loop FiO2 systems.

To conclude infants are vulnerable to both hypoxia and hyperoxia. In its nature it's hard to keep an infant within target especially when oxygen is manual titrated. How well the infants, cared for at our NICU in Växjö, are within SpO2 target range is unknown.

2. Purpose

NICU in Växjö has SpO2 target range of 90-95% regardless age and Fio2 is titrated manually by bedside nurses(25). All new nurses follow a training program called Olivia when they start working at the clinic and then follows local guidelines. The guideline for how to handle apnoea of prematurity was last updated 2019 and expired 2021 (3).

The purpose of this study is to investigate the proportion of time that infants receiving supplemental oxygen are within the target range for oxygen saturation set by the NICU in Växjö. This knowledge will constitute a baseline for the quality of care in Växjö and has never been done before. By extension it is important to improve the intensive care of infants through limiting the potential harm from repeated episodes of hypoxia and hyperoxia. The study will also give us background information for future upcoming discussions for improvements in the care, for example; Do NICU in Växjö need an updated training program? Do we need new guidelines? Should we use automatic closed loop FiO2 systems?

I hypothesize that it is impossible to keep infants within a target range 100% of the time. Based on the findings of Hagadorn et al., Laptook et al., van der Eijk et al. and Katleen et al., a reasonable proportion of time for the infants enrolled in this study to be within target range could be somewhere between 30-50%. I also hypothesize that nurses will aim for a higher saturation rather than a lower. Therefore, my theory is that the infants will spend more time above the target range than below.

My primary outcome is to measure the proportion of time infants in NICU in Växjö who are receiving supplemental oxygen are above, within and below predefined SpO2 target range 90-95%. Secondary outcome will be subgroup analyses. Are there any differences in keeping infants within target and above versus below target regrading; different ways of supporting respiration, different work shifts and workload for nurses.

3. Materials and Methods

3.1 Settings

Växjö Hospital is a regional hospital and the neonatal intensive care unit has a total of 11 beds available (7 family rooms and 4 emergency beds). Infants from 28 weeks of gestational or corrected age are cared for here. In 2022, 2041 live born children were born in Växjö, 224 of these were admitted to NICU. That's roughly 11% of the infants and is comparable with previous years. Although previous years the number of live born babies were approximately 2300 babies per year and approximately 260 needed neonatal care. NICU in Växjö sometimes also cares for out-region infants when other NICUs are fully coated. The neonatologists in Växjö can take care of infants born younger than 28 weeks of gestation, but the continuous care will often be at a university hospital (26). NICU in Växjö has a SpO2 target range of 90-95% regardless infants age (25). A few

numbers of infants might have a different target range because of underlying conditions and will not be included in the study.

3.2 Subjects

I plan to continuously recruit infants admitted to NICU whom receiving supplemental oxygen. Data collection will continue for 6 months with start in April 2024, with the goal of receiving 90 recordings. Infants eligible for participation will be all infants admitted to NICU, receiving supplemental oxygen regardless method and has a SpO2 target range of 90-95% regardless of gestational or corrected age and underlying conditions. Exclusion criteria will be infants having a different SpO2 target range or the supplemental oxygen are expected to be wind down the nearest hours. The recordings will be randomly made and each will cover a period of 24h. An infant can be studied several times, but no more then 4 times.

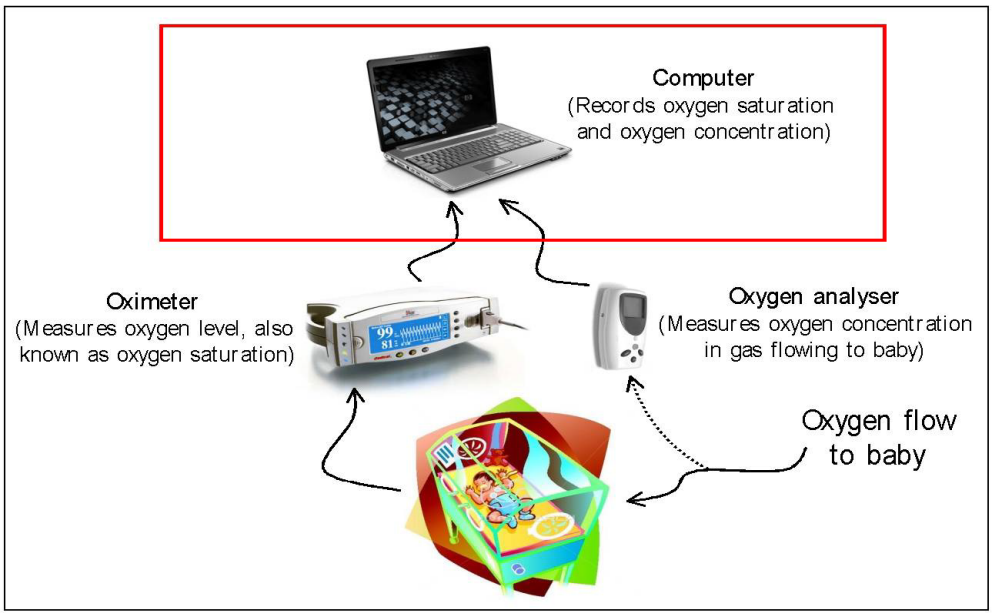
3.3 Instruments

3.3.1 Pulse Oximeter

I will use data from the ordinary pulse oximeter as part of the usual bedside monitoring system. There won't be any extra equipment put on the infant. A Masimo Pulse Oximeter (Rad 4 with LNOP sensor, Masimo Corporation, Irvine, USA) with a saturation accuracy of ± 3% will be placed on the infants' wrist or ankle to collect SpO2 data as in the usual care. The oximeter will be set to collect data continuously every two seconds with a maximum sensitivity. The pulse oximeter will be connected to the observation screen. From the observation screen data will be downloaded to a computer for analysis.

3.3.2 Oxygen analyser

An oxygen analyser will be connected into the infants breathing circuit to measure FiO2. The FiO2 data will be collected in an analogue format from the inline oxygen analyser (model MX 300-I, Teledyne Analytical Instruments, City of Industry, USA) to the laptop computer via an analogue-digital convertor box (NI USB-6259, National instruments, Austin, USA).



3.4 Data collection

The computer software program Spectra will be used to collect data. The data will consist of perfusion index, heart rate, SpO2 and FiO2. The data collected in Spectra will then be converted to an Excel file. I will also collect data on infant characteristics such as gestational age, corrected age, birth weight, current weight, method for respiratory support, diagnoses and where the pulse oximeter is placed (pre- or postductal) and the number of infants one nurse cares for (workload).

3.5 Infant management

Data will be collected for periods of 24h and cover three work shifts. The nurses will continue with their normal care of the infants and that information will be able to collect from the bedside chart. The nurses will change position of the pulse oximeter as in their usual care of the infant.

3.6 Data analyses

I will use help from a statistician doing the analyses of the data.

4. Consent

I will need to apply for consent by the Ethics Committee. After careful consideration I find no obvious ethical problems for the infants taking part in the study. My research does not interfere with, or change, any aspect of patient care. There is no risk for the infant and it won't lead to any physical harm. To respect the integrity of the enrolled no data collection will allow identification of individual infants. Furthermore, all data will be presented at group level to even more prevent

identification. Therefore, I assess the risk of privacy breach low. All data will be handled according to GDPR. An information leaflet will be given to parents and nurses explaining what data will be collected and for what purpose. Written consent from the parents will be obtained.

5. Timeframe

Data will be collected continuously for 6 months with start in April 2024. The project will be finished by the end of 2024.

Attachments

Information leaflet given to parents and nurses

Bedside protocol

Local guideline for apnoea of prematurity

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