Oxygen therapy in preterm infants: recommendations for practice

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Abstract

Oxygen is one of the most commonly used therapies in neonatology but optimum oxygen saturations for preterm infants have been debated for the past 50 years. The history of oxygen use in this population and multiple clinical trials over the years have shown that liberal oxygen administration is associated with retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) whereas restrictive use results in increased mortality and neurodisability. Pulse oximetry (SpO_2) is a bedside tool to guide the fraction of inspired oxygen (FiO_2) delivered to the patient, and is the current standard of care for continuous monitoring. Although evidence favours targeting predetermined oxygen saturation ranges, achieving this goal consistently in clinical practice has been challenging due to intrinsic pulmonary immaturity, the need for respiratory support therapies and factors relating to the bedside caregivers ability to adjust FiO_2. This review article focuses on the difficulties of titrating oxygen therapy in this vulnerable group and provides recommendations for the best practice based on up to date evidence.

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Keywords bronchopulmonary dysplasia; hyperoxia; hypoxia; oxygen; preterm; retinopathy of prematurity; saturation targeting

Introduction

Priestley, along with Scheele and Lavoisier in 1770s discovered that the air we breathe is really a mixture of 'vital' air and 'gas azote'. Later, Wilson et al., in 1940s made an observation that irregular pattern of periodic breathing, commonly seen in premature babies was overcome when they were given >70% oxygen. Since then there have been wide pendulum swings regarding the use of oxygen therapy in neonates.

Indiscriminate administration of oxygen led to the epidemic of retinopathy of prematurity (ROP) in the mid-20th century followed by an increase in deaths and cerebral palsy in the subsequent decades due to restrictions placed on oxygen delivery. Despite availability of various technologies, it is now accepted that pulse oximetry (SpO_2) is the most appropriate bedside tool to guide the fraction of inspired oxygen (FiO_2) delivered to the patient. The visual assessment by clinicians has a limitation of being highly unreliable and frequent blood gas assessments are not practical in the preterm infant.

Uncertainty prevailed regarding oxygen therapy and the ideal saturation targets until the recent large collaborative trials. The meta-analysis, combining data from nearly 5000 extremely preterm infants enrolled in oxygen targeting studies across 5 countries (NeOProM: Neonatal Oxygen Prospective Meta-analysis) reported that targeting higher (91%–95%) compared with lower (85%–89%) oxygen saturations had no significant effect on the composite outcome of death or major disability or on disability alone (including blindness).

However, when mortality was assessed in isolation, there was significantly increased survival in the high SpO_2 target group. This has resulted in most guidelines in the neonatal units around the world favouring the higher oxygen saturation target range as used in the NeOProM collaboration. Despite ongoing efforts, clinicians have struggled to keep infants in the prescribed targets, highlighting the need for novel approaches to mitigate this challenge.

Physiology of oxygen toxicity

In simple terms, oxidative stress is caused by the imbalance of deficient antioxidant defences in the setting of abundant generation of oxidants, leading to the production of free radicals and cell damage. The biochemical reactions involved at the molecular level are far more complex and dynamic. Premature neonates are susceptible to significant oxidative stress during the transition from a hypoxic *in utero* environment to the relatively high oxygen exposure after birth.

The main oxygen free radicals or reactive oxygen species (ROS) implicated in oxygen toxicity are superoxide anion ($O_2^{\cdot -}$), hydroxyl radical (OH^-) and hydrogen peroxide (H_2O_2), which have the capability to oxidize unsaturated free fatty acids, proteins and DNA. ROS are formed during the electron reduction of O_2 to H_2O. ROS excess in combination with an impaired antioxidant response leads to the common morbidities noted in preterm infants-retinopathy of prematurity, chronic lung disease,

Interventions for improving oxygen saturation targeting in NICU

Intervention	Components	Implementation methods
Evaluation of local challenges	Percentage of time SpO_2 above or below target range	Bedside monitor SpO_2 Histogram audit
	Frequency in occurrence of hyperoxaemia after apnoea and bradycardia events	Audit of apnoea and bradycardia events
	Day shift versus night shift differences	Evaluate local data
	ROP rates	
Policy/guideline/protocol development	SpO_2 targets and alarm limits	Creation of policy/guideline/protocol
	Titration of oxygen, pre-oxygenation	
	Histogram to evaluate oxygen usage or guide oxygen titration	
Education + policy/guideline/protocol implementation	Co-morbidities associated with low and high saturations targets and rapid fluctuations in saturations	Small group sessions
	Policy/guideline/protocol education	Grand rounds
	Importance of SpO_2 targeting	Instructional video
	Local challenges	Visual cues: cards at beside or on clipboard
	Histogram interpretation	Bedside training by super users
		Pre and post education tests
		Multidisciplinary team focus-Physicians, Nurse Practitioners, Nurses, Respiratory Therapists
Compliance monitoring	SpO_2 alarm limits	Oxygen saturation alarm limit audits
	Histogram to evaluate oxygen usage or guide oxygen titration	Assessment of time in SpO_2 target range using bedside monitor histogram data

Table 1

periventricular leukomalacia (PVL), intraventricular haemorrhage (IVH) and necrotising enterocolitis (NEC).

Antioxidants are typically electron donors that inhibit or repair oxygen mediated injury. Glutathione (GSH) is the most abundant antioxidant in the body but is synthesised only in the third trimester, which puts very preterm infants at increased risk of damage. Superoxide dismutases (SOD's), thioredoxin and heme oxygenases are the other antioxidant defence systems that play an important role. It would seem physiologically plausible that supplementation with these antioxidant substances might prevent or even reverse the ROS mediated damage in preterm infants. However, studies looking at supplementation with GSH precursors like cysteine chloride and N-acetylcysteine has not shown significant benefit. Further research should ideally include evaluations of the prognostic and therapeutic value of oxidative stress biomarkers and antioxidants in the premature infants. The role of mitochondria, which is the key site of these redox reactions also merits further evaluation.

Measurement and monitoring of oxygenation in preterm infants

The commonly available tools for monitoring oxygenation in preterm infants on the NICU are pulse oximetry, arterial blood gas analysis and rarely transcutaneous partial pressure of oxygen ($TcPO_2$) measurement. More recently, there has been growing interest in monitoring end organ perfusion and oxygen delivery utilising cerebral and somatic Near Infra Red Spectroscopy (NIRS).

Arterial blood gas (ABG) analysis

Monitoring of tissue oxygenation by measuring partial pressure of oxygen in arterial blood (PaO_2) is considered the gold standard surrogate of tissue oxygenation in preterm infants. However, PaO_2 monitoring is hampered by the requirement of an invasive indwelling catheter that cannot be maintained long term and the limited information obtained from intermittent point assessments.

Transcutaneous oxygen monitoring ($TcPO_2$)

$TcPO_2$ electrodes measure the partial pressure of oxygen dissolved in blood through the skin, using a sensor which is heated up to 42–44 °C. There is the additional advantage of continuous transcutaneous CO_2 ($TcPCO_2$) monitoring utilising the same equipment. The clinical use of this modality has been largely superseded by pulse oximetry due to various factors like the need for regular calibration and local complications such as skin burns, particularly in extreme preterm babies.

Pulse oximetry (SpO_2)

SpO_2 measurement is based on the principle of pulsatile variations in optical density of tissues in the red and infrared wavelengths to compute arterial oxygen saturation and this correlates with the proportion of oxygenated to deoxygenated haemoglobin. Reliable SpO_2 tracings in preterm infants can be facilitated when the light receiving diode is placed opposite to the emitting diode and avoiding excessive pressure while applying the probe. Shielding the oximeter sensor site from bright ambient light and phototherapy light has also been recommended by certain neonatal guidelines, as it was perceived to interfere with obtaining accurate

readings. However, a recent study reported that this practice did not yield faster data acquisition or better data quality.[1] The wrist, palm and foot are the usual sites for applying the pulse oximeter probes; with right extremity pre-ductal placement providing the best guide of oxygen delivery to the brain.

Advantages of SpO_2 monitoring include its widespread availability in most neonatal settings, non-invasive continuous readouts, which is available immediately without the need for calibration and the detection of rapid fluctuations in oxygen saturations.

However, pulse oximetry does have technical limitations. Its measurement is hampered by motion artefacts, electromagnetic interference and there are physiological limitations. These include hypotension, hypoperfusion, severe anaemia and haemoglobinopathies e.g. methaemoglobinemia.

Advances in modern pulse oximeters have significantly mitigated some of these factors. However, the relationship between SpO_2 and PO_2 is not linear, especially with regard to accuracy and reliability of reflecting true arterial PO_2 at the extremes of oxygen saturations (see Figure 1).

Possible adverse effects of oxygen in preterm infants

Retinopathy of prematurity (ROP)

Vascularization of the retina is primarily affected by Vascular Endothelial Growth Factor (VEGF) and Insulin like growth factor-1 (IGF-1). VEGF release is increased in the presence of hypoxia, which is the norm *in utero*. Increased oxygen levels after preterm birth halts retinal vascular growth and regression of vascularization begins due to vasoconstriction of the immature retinal vessels. Around the 32–34 week PMA stage, the retina grows in thickness resulting in the gradual development of localised retinal hypoxia leading to neovascularisation from excess of VEGF release, causing ROP. Retinal detachment is a dreaded complication that occurs in the setting of uncontrolled proliferative retinopathy. Widespread adoption of higher saturation targets in NICU (91–95%) has resulted in increased rates of ROP requiring treatment, but due to effective implementation of screening protocols in developed countries, incidence of blindness has not worsened.

Bronchopulmonary dysplasia (BPD)

Although barotrauma from mechanical ventilation is commonly associated with BPD, excess oxygen exposure also plays a major role in preterm infants. Oxidative stress has been implicated to have a direct toxic effect on the bronchial and alveolar epithelium as well as capillary endothelium in both animal and clinical studies. The injury manifests as alveolar oedema, neutrophil infiltration, proliferation of alveolar cells and finally the characteristic fibrotic changes associated with BPD. Premature infants are more prone to oxidative stress as they have a higher risk of exposure to high oxygen concentrations, reduced antioxidant defence and more free iron leading to production of hydroxyl radicals.

Preterm brain injury

White matter in the brain of premature infants is vulnerable to oxidative damage. This vulnerability is because of four main factors: the high content of unsaturated free fatty acids which are easily exposed to peroxidation, the presence of free iron, low levels of antioxidant enzymes, and vulnerable oligodendrocytes. There is a higher propensity for preterm brains to be exposed to hyperoxia as well as inflammation, which increases oxidative stress and results in periventricular leukomalacia. Intraventricular haemorrhage is frequently seen in extremely premature infants due to ischemia from an initial hypoxic hit followed by ROS mediated hyperoxic reperfusion injury, after circulation has been restored.

Neonatal haemolytic anaemia

Newborn erythrocytes are more susceptible to oxidative damage resulting in haemolysis, more so in preterm infants. High concentration oxygen also exerts a toxic effect on red cell membranes leading to changes in erythrocyte shape.

Oxygen targeting

Stabilisation at birth

Preterm newborns frequently require support to establish respiration at birth due to various factors including surfactant deficiency, weak respiratory muscles and immaturity of the elastic thoracic cage. Positive pressure support and supplemental oxygen are the key interventions to facilitate this transition. There is nearly tripling of PaO_2 during the adaptation from fetal placental circulation to *ex utero* breathing at birth. The immature antioxidant defence system of extremely preterm infants is particularly ill equipped to handle this surge in oxidative stress.

While there is reasonably robust evidence for commencing resuscitation in room air for term infants, uncertainty remains regarding the ideal starting FiO_2 in preterm neonates. As recently as 2005, administration of 100% oxygen was virtually universal for the respiratory support of extremely low birth weight infants in developed countries at the time of birth. However, delivery room studies reported resuscitation of preterm neonates with 30% oxygen compared to 90% caused less oxidative stress, inflammation and reduced the risk of BPD. This highlighted the need to target an appropriate SpO_2 range even in the first minutes after birth. Current newborn resuscitation guidelines recommend titration of oxygen therapy guided by pre-ductal pulse oximetry and utilising SpO_2 reference ranges to account for the escalating oxygen saturation values over the first 10 minutes of life.

This gradual increase in SpO_2 seen at birth, is the time taken to aerate the lungs, extrude fetal lung fluid and establish functional residual capacity. Only a minority of resuscitation guidelines have gestation specific SpO_2 targets even though there is consensus regarding a starting FiO_2 of 30%. This guidance is not strictly evidence based but an ongoing multicentre RCT comparing both short and long term effects of a starting FiO_2 of 30 vs 60%, in extremely premature newborns should shed some light on this conundrum. Although SpO_2 nomograms have been published for preterm infants <32 weeks gestation transitioning at birth, this is based on data from only 39 babies.[2] In the absence of definitive data, experts recommend aiming for a SpO_2 of at least 80% at 5 minutes of age, as there is an association with increased mortality and intraventricular haemorrhage in preterm infants who do not achieve this target.

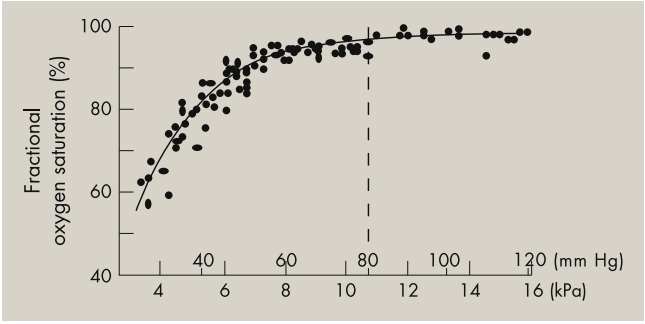

Figure 1 Relationship between fractional oxygen saturation measured with a pulse oximeter and arterial partial pressure in mmHg and kPa. The dashed line marks the transcutaneous PO2 above which there was an increased risk of retinopathy. Reproduced with permission from: Tin W, Gupta S. Optimum oxygen therapy in preterm babies. Arch Dis Child Fetal Neonatal Ed. 2007 Mar; 92 (2): F143–F147.

Care on the NICU

Outcomes from prospective meta-analysis of 5 large oxygen saturation targeting trials in premature infants using harmonised individual patient data (NeOProM Collaboration) has raised awareness about the importance of maintaining SpO_2 within a narrow prescribed range. There was increased mortality and NEC in the low oxygen saturation target group (85–89%) compared to the high SpO_2 group (91–95%). Even though there was an increase in BPD and ROP requiring intervention in the high SpO_2 arm, there was no significant difference in home oxygen requirement or severe visual impairment amongst both groups. Following these results, a recent international survey of NICU's showed that an oxygen saturation target of 90–95% was commonly recommended by local guidelines. Clinicians should ideally aim to titrate supplemental oxygen therapy to maximize the amount of time spent in the appropriate target oxygen saturation range, taking care to avoid prolonged periods of either hypoxemia or hyperoxemia as a trade-off.

It has been shown that bedside clinical staff tend to have a higher tolerance for hyperoxia than hypoxia. This is reflected in the oxygen saturation targeting trials, where both high and low saturation target groups ended up with higher than intended oxygen saturations.

Oxygen targeting is particularly challenging in extremely preterm infants and those with established chronic lung disease, mainly due to a combination of apnoea causing intermittent hypoxemia and parenchymal lung changes resulting in significant ventilation perfusion disturbances (Box 1). Intermittent hypoxemia and rapid fluctuations in oxygen saturation have been shown to be highly predictive of ROP with increased risk of neurodevelopmental impairment. Mode of oxygen delivery may also play a role with hyperoxia, more likely in infants on low flow oxygen rather than non-invasive positive pressure (NIPPV)/continuous positive airway pressure (CPAP) support; although it could be argued the latter group was probably more unwell. This may also be due to the limitations of accurately titrating oxygen delivery on a flowmeter compared to an air/oxygen blender.

Interventions to improve oxygen saturation targeting in the NICU should focus on patient related variables as well as multiple human factors that affect this critical metric. These include, inadequate staffing, lack of awareness regarding institution saturation targets, higher tolerance for hyperoxia and alarm fatigue resulting in widening of alarm limits (Figure 2).

Intensive caregiver training seems to be the most effective means to improve SpO_2 targeting. This may include formalising and socialising agreed target ranges amongst bedside clinical

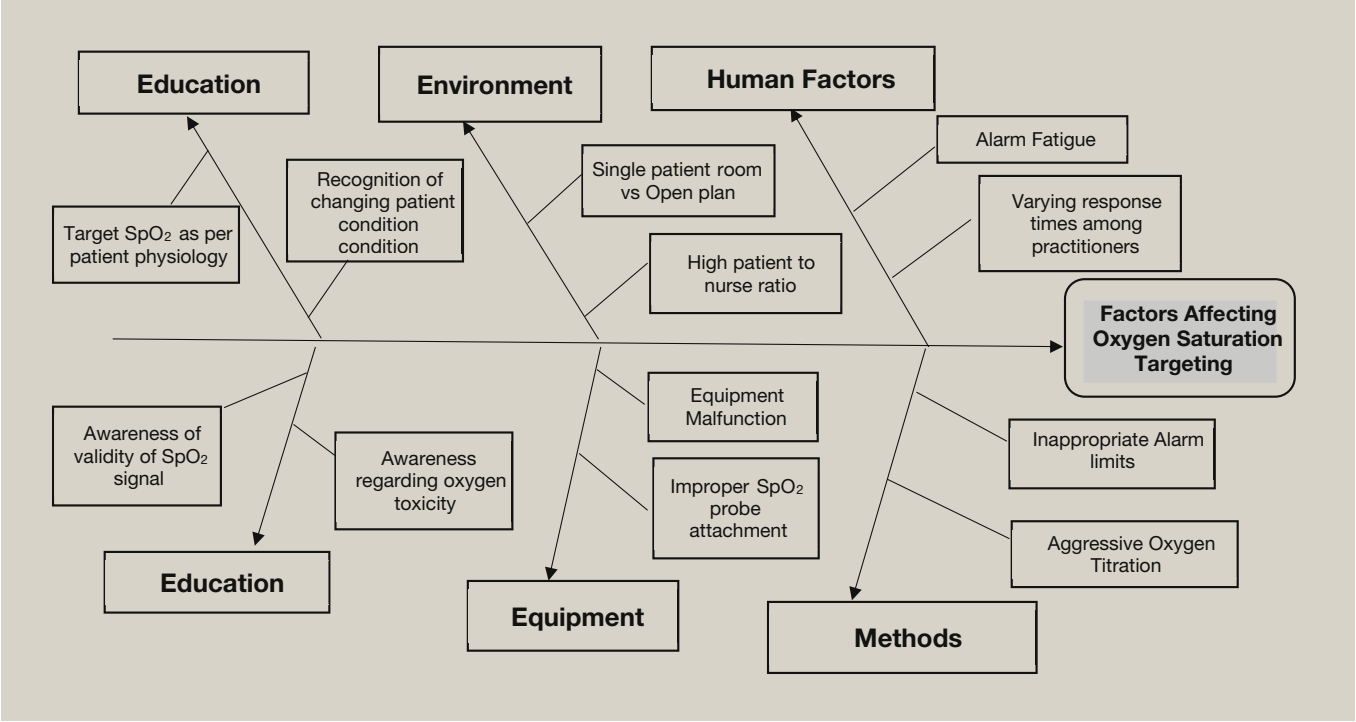

Figure 2 Cause and effect diagram showing factors affecting oxygen saturation targeting.

Physiological factors causing fluctuation of oxygenation in preterm infants

1. Immature respiratory control resulting in apnoea and respiratory pauses
2. Airway obstruction
3. Periodic breathing pattern which peaks at 2–3 weeks post-natal age
4. Low lung volume or FRC due to increased chest wall compliance and atelectasis
5. Pulmonary hypertension and hypoxia induced vasoconstriction
6. Ventilator asynchrony and splinting episodes
7. Respiratory equipment malfunction or interface displacement
8. Anaemia resulting in decreased oxygen carrying capacity and stores

Box 1

staff, ensuring consistent setting of bedside monitor alarm limits, implementing oxygen titration protocols and using SpO_2 histogram data to objectively monitor oxygenation trends (Table 1 and Figure 3).

Future developments

Closed loop automated oxygen control at birth and in NICU

A significant proportion of preterm infants require respiratory support and supplemental oxygen at birth. Pulse oximetry and oxygen blenders to adjust FiO_2 are a part of routine care in most tertiary delivery room settings. Observational studies have shown that preterm infants spend only 30–50% of the time within the desired target range in the first 10 minutes of life. This can be partly explained by the immature respiratory drive and

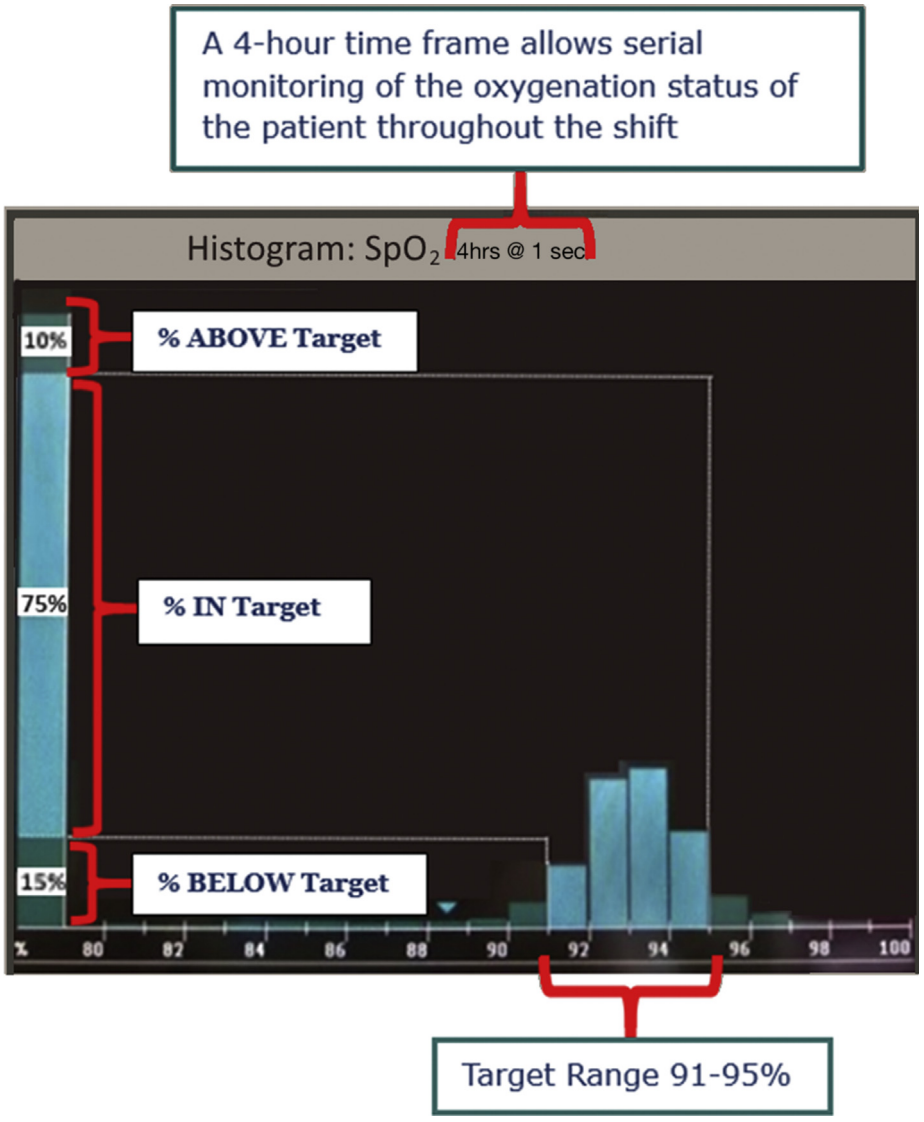

Figure 3 Example of SpO_2 histogram from the bedside monitor, which shows a significant proportion of time spent in target range (91–95%) with minimal time spent in the extremes of oxygenation.

Recommendations/practice points for minimising oxygen toxicity in preterm infants

At birth

- Commence resuscitation with FiO_2 of 30% pending evidence from ongoing trials investigating this issue.
- Follow escalating oxygen saturation nomograms for the first 10 minutes of life as per local resuscitation guidelines but target preductal SpO_2 of at least 80% at 5 minutes of age.

In NICU

- Optimise baseline oxygen saturation utilising appropriate invasive or non-invasive respiratory support.
- Caffeine administration to reduce apnoea of prematurity and minimise fluctuation in oxygen causing both hypoxemia and hyperoxemia.
- Adopt a target range of 91%–95% for oxygen saturation in infants less than 28 weeks' gestation
- Implementation of the higher target range should be accompanied by close surveillance for the prevention and early treatment of ROP.
- Improvement in oxygen saturation targeting can be brought about by focusing on caregiver training at the bedside and by providing adequate staffing.
- Closed loop automated oxygen control improves time spent in oxygen saturation range but its effect on reducing long term morbidity or mortality is unknown.

Table 2

surfactant deficiency. In addition, the resuscitating team is likely to focus on stabilising the airway and initiating breathing rather than titration of oxygen. Animal studies using purpose built automated oxygen control algorithms to target the escalating SpO_2 range in the first 10 minutes of life has shown promise, but needs validation by clinical trials in neonates.[3]

Preterm infants on supplemental oxygen in NICU, usually spend half their time outside the prescribed target range. In addition to the complications associated with hyperoxia like ROP and BPD, intermittent hypoxemia is commonly seen in extremely preterm infants and is strongly associated with adverse neurodevelopmental outcome.

Closed loop automated control of oxygen therapy in NICU is not a new concept and has been around for a few decades. Multiple clinical trials have confirmed the efficacy of automated oxygen control to target a prescribed SpO_2 range, compared to manual adjustment by clinicians. It also decreases exposure to extremes of oxygenation and reduces the need for manual adjustments by bedside staff. Although control algorithms have been incorporated in many commercially available neonatal respiratory support devices, it has not yet been established in routine clinical care. The short term benefits appear obvious, but studies focused on long term outcomes are needed before closed loop automated oxygen control is established as the standard of care in neonates (Table 2).

Near infra-red spectroscopy (NIRS)

NIRS is a useful non-invasive clinical tool for assessing end organ perfusion and the balance of oxygen delivery and consumption. It is based on continuous spectrometric measurement of oxygen dependent changes in the absorption properties of the chromophores, haemoglobin (Hb) and cytochrome aa3, in the near infra-red range. NIRS has been extensively studied in preterm newborns and measures oxygenated Hb in the tissues whereas pulse oximetry measures oxygenated Hb in the pulsatile blood vessels.

NIRS offers the possibility of titrating oxygen and haemodynamic supports to optimise oxygen delivery at the tissue level and thereby prevent complications associated with hypoxia and hyperoxia. This needs validation by large clinical trial assessing clinically important outcomes.

Conclusion

Despite multiple studies, the ideal oxygen saturation target range for preterm infants, both at birth and in the NICU, which would allow maximal survival and minimise the risk of neurosensory impairment continues to be elusive. However, efforts should be made to decrease exposure at the extremes of oxygenation in this vulnerable population. ◆

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