CE 2.5 HOURS Continuing Education

Oxygen Administration to Preterm Neonates in the Delivery Room

Minimizing Oxidative Stress

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ABSTRACT

Background: Neonatal resuscitation continues to be challenged by evolving research on the best approach to resuscitating preterm infants while minimizing potential health risks. The actions of the resuscitation team in the first minutes of transition to extrauterine life can have a lasting impact on the growth and development of the preterm infant.

Purpose: This article reviews the most current literature on the use of oxygen in the delivery room and discusses the implications related to nursing and the multidisciplinary care team.

Findings: Oxygen saturation monitoring in the delivery room through the use of pulse oximetry in conjunction with oxygen titration via a blended oxygen source is an appropriate intervention to decrease the risk of free radical damage to the tissues.

Implications for Practice: Ensure delivery room providers are educated to resuscitation standards and ensure delivery rooms are appropriately supplied with a compressed air source, oxygen blenders, and pulse oximeters to minimize the free radical damage to the tissues.

Implications for Research: Future studies should be focused on pulse oximetry use in the delivery room and its effect on long-term outcomes for preterm infants, safe oxygen saturation target ranges for the preterm infant in the delivery room, and effective resuscitation procedures for extremely preterm infants.

Key Words: chronic lung disease, CLD, FIO_2, free radicals, hyperoxia, neonatal resuscitation, oxygen saturation, preterm neonate, reactive oxygen species, SpO_2

PROBLEM STATEMENT

The administration of supplemental oxygen to preterm infants in the delivery room is a challenging multidisciplinary intervention among the medical team, nursing team, and respiratory therapy team that can have adverse outcomes for the infant. Preterm infants have a physiologic challenge in achieving sufficient gas exchange at birth due to surfactant deficiency, immature lung development, poor respiratory drive, and poor clearance of lung fluid, which may make oxygen administration unavoidable.[1-4] Exposing a preterm infant to oxygen even for a brief amount of time has a potential to cause a chain of oxidative stressors that can last for weeks after the exposure and make the best neonatal care challenging.[5-7]

A free radical is a highly reactive atom or molecule that contains 1 or more unpaired electrons.[8-12] Oxygen has 4 electrons, 1 pair being shared and 2 others that remain single as free radicals. This triggers a chain reaction that generates a superoxide radical, the hydroxyl radical, and the hydrogen peroxide radical. These oxygen free radicals are collectively referred to as reactive oxygen species (ROS).[8-12] Oxidative stress occurs when there are more ROS than the antioxidant system (AOS) can handle. This can be due to increased ROS production or an inadequate AOS.[9-10,12] Retinopathy of prematurity (ROP), chronic lung disease (CLD), intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL) have been identified as comorbidities associated with ROS and fall under oxygen radical diseases of the newborn, with CLD being the most costly morbidity.[5,9,10,12-16] This literature review examines the use of oxygen in the delivery room for the resuscitation of preterm infants and strategies that can be implemented to reduce oxidative stress from ROS in the first several minutes of life.

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BACKGROUND

The cardiopulmonary transition from intrauterine to extrauterine life at birth involves several critical physiologic factors that start late in fetal development and during the onset of labor. In a healthy newborn, mobilization of lung fluid, expansion of the airways and alveoli, a decrease in pulmonary vascular resistance, constriction of the ductus arteriosus and ductus venosus, and an increase in peripheral vascular resistance begin with the initial crying. Blood oxygen levels increase with a subsequent decrease in vascular shunts and closing of the ductus arteriosus and ductus venosus.[4,17] An important component in the cardiorespiratory transition is establishing functional residual capacity by getting air, not oxygen, into the fluid filled lungs. Establishing a normal functional residual capacity will allow for optimal lung mechanics and alveolar surface area for effective ventilation and gas exchange.[1,4,12]

Transition to extrauterine life for a newly born infant involves going from a hypoxic environment to a hyperoxic environment. The newly born infant must have physiologic mechanisms in place to efficiently adapt from an oxygen environment of a partial pressure of oxygen of 20 to 25 torr to an environment with a partial pressure of oxygen of 100 torr.[7,12,16,18] The AOS is an oxygen free radical defense system consisting of several enzymes that target the destruction of the superoxide, hydroxyl, and hydrogen peroxide free radicals. The AOS includes superoxide dismutase (SOD), catalase, glutathione peroxidase, ceruloplasmin, ascorbic acid, vitamin A, vitamin E, and transferrin.[8,10-12,18] The up regulation of antioxidants in the fetus starts late in gestation and parallels the pulmonary development of the fetus.[9,11,12,15,18] An important consideration with preterm infants is that surfactant contains a significant amount of SOD and catalase, 2 important antioxidants.[18] Preterm infants are deficient in surfactant, which not only interferes with the AOS, but also the establishment of functional residual capacity required for effective ventilation and gas exchange.[16,17]

Preterm infants are at an increased risk for tissue damage from ROS due to increased ROS production, a diminished AOS defense system, impaired ability to up regulate antioxidants enzymes in response to injury, and the sensitivity of rapidly growing tissues to ROS.[5,9-12,14,16-20] Ensuring adequate delivery of oxygen to the tissues with the least amount of oxygen exposure is the most important goal of neonatal resuscitation.[17] To meet this goal, some suggest that there is a target oxygen saturation (Spo_2) protocol in the delivery room along with pulse oximeters, oxygen blenders, and compressed air sources.[3,6,13,16,17,21-23]

The administration of oxygen in the delivery room depends on the gestational age of the infant and other variables that may lead to decreased oxygenation to the tissues. Delivery complications or maternal factors such as abruption can lead to blood loss that will in turn require fluid volume support to enhance cellular oxygenation. This is an important factor to consider as the use of supplemental oxygen will be meaningless without adequate blood volume and will cause unnecessary oxygen exposure to the neonate.[17] The use of oxygen in the delivery room is of great importance because brief exposures of oxygen in the delivery room can cause oxidative stress that can last for 4 weeks after birth. This will make even the best NICU care challenging.[5-7] Comorbidities associated with hyperoxia, such as ROP, CLD, IVH, and PVL, can reduce the quality of life and place an emotional and financial burden on the family and health care system.[5,9,10,12-16] There have also been studies associating brief exposures of oxygen in the delivery room to childhood cancer and leukemia.[7,24,25] The NICU team in the delivery room has an obligation to the fragile preterm infant to be cognizant of oxygen use and provide a synergy of optimal cellular oxygenation needed for growth and development.

FRAMEWORK

This review of literature is guided by the framework of Ola Saugstad's free radical production and oxygen paradox theory. Saugstad describes 2 mechanisms in which free radicals can be formed in the lung.[11] They are respiratory bursts in phagocytizing cells and through the hypoxanthine-xanthine oxidative system.[11,15] When a neutrophil is exposed to bacteria, the oxygen uptake of the neutrophil is increased as much as 50-fold. Consequently, a large amount of superoxide radical and hydrogen peroxide are produced by the activation of an enzyme that catalyzes the unpaired reduction of oxygen to superoxide radical. This is called the respiratory burst.[11]

More relevant to this review of literature is the second mechanism of free radical production that Saugstad refers to as the hypoxanthine-xanthine oxidative system.[11,15] Hypoxanthine is produced during hypoxia and is then washed out into the circulation during reoxygenation producing free radicals.[11,15] Xanthine oxidase is the enzyme responsible for the process of the hypoxanthine producing free radicals through conversion of the oxygenase form shortly after hypoxia or release from the liver.[11] This phenomenon is described as the oxygen paradox, in which hypoxanthine accumulates during hypoxia, oxygen is administered as a treatment modality, and large amounts of oxygen radicals are assumed to be formed.[11,15] This has been used as a hypothesis to describe oxygen radical diseases in neonatology by

Saugstad, such as CLD, ROP, and necrotizing enterocolitis.[15] This framework was chosen because free radical formation during hypoxia is an important consideration when utilizing oxygen during resuscitation since even more free radicals can be generated leading to lung damage.

REVIEW OF LITERATURE

Harling et al[26] conducted a randomized control trial with factorial design on 52 infants less than 31 weeks' gestation to investigate if the amount of oxygen used during resuscitation at birth triggers events that lead to subsequent lung injury. The authors also investigated whether a reduction in oxygen used would lead to a reduction in lung injury.[26] They found no significant difference in bronchopulmonary dysplasia (BPD) in infants resuscitated with 100% fraction of inspired oxygen (Fio_2) or 50% Fio_2. They determined that there was no danger in resuscitating with 50% Fio_2 but no clear benefit either.[26] This study demonstrated that resuscitating preterm infants with a lower oxygen concentration does not harm, or benefit, the preterm infant, and that more research is needed on the long-term effects of oxygen toxicity.

Deulofeut et al[27] performed a detailed analysis of a prospectively collected database of 502 infants weighing 1250 g or less to analyze if infants in an Spo_2 target range of 85% to 93% would have similar rates of mortality compared with those infants in an Spo_2 target range of 92% to 100%. The authors found that the mortality rate was the same during both periods ($P = .81$). The length of stay, the treatment for CLD, and the rate of ROP were significantly lower in the 85% to 93% target range ($P < .05$). The distribution of IVH and PVL was similar between the 2 groups ($P = .5$ and .6, respectively). Neurodevelopmental outcomes were similar between the 2 groups. This study provides support that approximately 6 new cases of CLD, 9 cases of stage II ROP, and 3 cases of stages III to IV ROP can be prevented for every 100 infants with birth weights of less than 1250 g by targeting lower Spo_2 limits.[27] This study relates more to the chronic phase of neonatal care versus interventions in the delivery room, but the findings can be applied to avoid hyperoxemia in the first minutes after life to reduce the possibility of free radical formation.

Escrig et al[22] conducted a randomized clinical trial on 42 infants 28 weeks' gestation or less to demonstrate that it is possible to achieve a target Spo_2 of 85% at 10 minutes after birth by using 30% Fio_2 as it is using 90% Fio_2. The authors sought to prove that by using 30% Fio_2 initially could reduce the oxygen load administered in the first critical minutes of postnatal life.[22] This study found that there were no differences in Spo_2 between the 2 groups at 4 minutes after cord clamping, and both groups reached a stable Spo_2 of 85% at 5 to 7 minutes of life. There were no differences in mortality between the 2 groups. The higher oxygen groups showed a tendency of increased BPD and ROP at the time of discharge but were not significant ($P = .065$ and .069, respectively).[22] This study adds to the concern about free radical formation by demonstrating that resuscitating preterm infants at a lower Fio_2 of 30% reduces the oxygen load and allows infants to be ventilated with an Fio_2 as low as 30% after clinical stabilization. This could reduce oxygen radical diseases associated with hyperoxia and excessive oxygen administration during resuscitation in the delivery room.

Wang et al[23] performed a prospective, dual center, randomized controlled clinical trial on 41 infants 23 to 31 weeks' gestation to evaluate the use of room air for resuscitation of preterm infants. The authors sought to prove that resuscitation of preterm infants initiated with room air and adjusted on the basis of Spo_2 levels would be more effective than 100% oxygen in achieving Spo_2 values similar to those of nonresuscitated transitioning infants. This study found that preterm infants resuscitated with room air needed an increase in Fio_2 by 3 minutes of life, and the room air group had significantly lower Spo_2 values between 2 and 10 minutes of life ($P = .01$). There were no differences in heart rate between the 2 groups. Wang et al[23] hypothesized that a target approach might be most successful in resuscitation, with a starting point somewhere in the middle of 21% and 100% Fio_2. This study provides support for the practice of titrating oxygen based on Spo_2 readings to promote minimal free radical formation and guide future research since the optimal Spo_2 values for preterm infants remain variable.

Dawson et al[21] performed a prospective observational study on 126 infants less than 30 weeks' gestation to describe changes in preductal Spo_2 and heart rate in the first 10 minutes after birth in those preterm infants initially resuscitated with 100% oxygen or air. There was no specified level of significance for their findings. Dawson et al[21] found that the Spo_2 of preterm infants resuscitated with 100% oxygen were 60%, 84%, 94%, and 96% at 1, 2, 5, and 10 minutes, respectively. The preterm infants resuscitated with room air had Spo_2 of 55%, 31%, 54%, 81%, and 91% at 1, 2, 5, 6, and 10 minutes, respectively. The heart rates of both groups were similar throughout resuscitation. These findings suggest that starting with a high Fio_2 to resuscitate an infant may cause a quick onset of hyperoxia. Dawson et al[21] suggest that by monitoring Spo_2 in the delivery room and titrating Fio_2 accordingly may assist in preventing hyperoxia. In addition, since heart rate is the most important factor in evaluating the effectiveness of resuscitation, starting at a lower

Fio_2 and adjusting needs accordingly can be acceptable, given that the heart rates in the 2 groups showed no significant difference.[21] This study relates to the problem of free radical formation during delivery room resuscitation by suggesting the use of pulse oximeters and Spo_2 monitoring to provide optimal tissue oxygenation without exposing developing tissues and organs to excessive oxygen and subsequent free radical production. [AU004]

Ezaki et al[13] conducted a blinded randomized controlled trial on 44 infants less than 35 weeks' gestation and delivered by cesarean section to determine the effects of the level of inhaled oxygen used during resuscitation on the levels of free radicals and antioxidative capacity in the blood of preterm infants. The authors measured total hydroperoxide levels, a representation of the total radical oxygen metabolites produced, and found this level to be higher in the 100% oxygen group versus the reduced oxygen (oxygen titrated based on Spo_2 readings) group ($P < .0001$).[13] The redox potential, or antioxidant potential, was not significantly different between the 2 groups ($P < .399$). The redox potential/total hyperoxide ratio was lower in the 100% group than in the reduced oxygen group ($P < .01$).[13] These findings support the use of pulse oximeters to monitor Spo_2 in the delivery room when oxygen is indicated in an effort to reduce oxidative stress in the premature infant.

Vento et al[20] conducted a prospective randomized controlled trial with 78 infants, who were 28 weeks' gestation or less, to test their hypothesis that lower Fio_2 levels during resuscitation would cause less oxidative stress and inflammation and would reduce the need for oxygen supplementation and mechanical ventilation and/or the incidence of BPD. The infants were divided into a lower oxygen group, which used an Fio_2 of 30%, and a higher oxygen group, which used an Fio_2 of 90%. The authors found that the low oxygen group needed fewer days of oxygen supplementation and had fewer days of mechanical ventilation ($P < .01$).[20] The low oxygen group had a lower incidence of BPD at discharge ($P < .05$). Reactive oxygen species biomarkers for oxidative stress were higher in the high oxygen group at day 1 ($P < .01$) and day 3 ($P < .05$). Urinary markers for oxidative stress were increased significantly in the high oxygen group in the first week after birth ($P < .01$). Markers for oxidative stress correlated significantly with the development of CLD ($P < .05$).[20] This study provides a vivid picture of the problem of increased oxygen use in the delivery room during resuscitation contributing to the development of ROS and the lung injury superimposed by free radicals. Through these findings, the careful monitoring of Spo_2 when administering oxygen in the delivery room is clearly validated to minimize free radical production.

Rabi et al[3] conducted a blinded, prospective, randomized control trial wwith 106 infants, who were 32 completed weeks' gestation or less, to compare 3 different oxygen titrating strategies to determine which one was the best in maintaining Spo_2 ranges of 85% to 92% during delivery room resuscitation of preterm infants. The 3 oxygen groups were divided into the high oxygen group (Fio_2 100%), the moderate oxygen group (start at Fio_2 100% and titrate based on Spo_2), and the low oxygen group (Fio_2 21%). The authors sought to prove that infants resuscitated with 21% Fio_2 would remain in the target Spo_2 range for the greatest proportion of time during resuscitation.[3] This study found that the 3 groups reached the target Spo_2 level in the same amount of time ($P = .56$-$.99$), but the low oxygen group had higher treatment failure rates despite rapid titration of oxygen ($P < .02$). Rabi et al[3] concluded that starting resuscitation with 100% oxygen with frequent titration was the most effective at reaching the target Spo_2 range while avoiding hyperoxemia. This adds to the research that titrating oxygen in the delivery room is an effective intervention to avoid hyperoxemia and the risk of overwhelming the tissues with free radicals from excessive oxygen administration.

The previous studies reveal a common theme in that recognition of Spo_2 after birth and titrating oxygen may help limit the amount of oxidative stress encountered by a preterm infant. The studies show some variances on the specific Fio_2 needed to initiate resuscitation. Gaps in knowledge include the optimal Spo_2 range to target during transition from fetal to neonatal life and a specific starting point for oxygen titration. The findings of the current research provide guidance for future research. Table 1 summarizes the research findings that link to care in the delivery room.

IMPLICATIONS

Oxygen is a double edge sword that is necessary for survival yet can be damaging in excess amounts.[6,8,11,12] This is a phenomenon in neonatology commonly referred to as the oxygen paradox.[11,12] Oxygen is completely available, easily diffuses across biological membranes and can bind to heme proteins.[8,12] Oxygen is reduced in the mitochondria to 2 water molecules and is catalyzed by an oxidase enzyme complex in an electron transport reaction.[28] The single oxygen atom is unstable, and therefore it tends to bond to a twin atom, forming molecular oxygen.[8] The stability of this bond is compromised because only 1 pair of electrons is shared and 2 electrons remain unpaired, forming a free biradical.[8] Two percent of oxygen consumed causes ROS.[7] Three free radicals, also referred to as ROS, can be formed from this electron transfer before oxygen is

TABLE 1. Summary of Evidence-Based Literature and Links to Care in the Delivery Room

Author	Purpose	Design/Sample	Key Findings	Links to Care in Delivery Room
Harling et al[26]	Investigate if the amount of oxygen used during resuscitation at birth triggered events that lead to lung injury	Randomized controlled trial 52 preterm infants less than 31 weeks' gestation	There was no statistically significant difference in BPD in those infants resuscitated with 100% F_{IO_2} vs 50% F_{IO_2}	There is no danger in resuscitating with a lower oxygen concentration, but no clear benefit either. Future research warranted
Deulofeut et al[27]	Investigate if infants in an 85%-93% Sp_{O_2} target range would have similar rates of mortality compared with those in a 92%-100% Sp_{O_2} target group	Detailed analysis of a prospectively collected database 502 infants weighing less than 1,250 g	Length of stay, CLD, and ROP lower in infants in the lower target group	NICU care starts in the delivery room and special attention to Sp_{O_2} is crucial in preventing hyperoxia in the first minutes of life. Avoiding a high saturation target in the delivery room can also help minimize free radical formation
Escrig et al[22]	To demonstrate that it was possible to achieve a target Sp_{O_2} of 85% at 10 min after birth as effectively by using 30% F_{IO_2} as by using 90%; this reduces the oxygen load in the first minutes	Prospective, randomized controlled trial 42 infants 28 weeks' gestation or less	Both groups reached a stable Sp_{O_2} of 85% at 5-7 min of life. There were no differences in Sp_{O_2} at 4 min after cord clamping. There were no differences in mortality. There was a tendency toward increased BPD and ROP in infants in the high oxygen group	Resuscitating infants at a lower F_{IO_2} can allow infants to reach an acceptable Sp_{O_2} with close Sp_{O_2} monitoring an oxygen titration. This reduces the overall oxygen load and risk for development of free radical diseases
Wang et al[23]	Evaluate the use of room air for resuscitation of preterm infants	Randomized controlled trial 43 infants with gestational ages between 23 and 31 wk	The room air group needed an increase in F_{IO_2} by 3 min of life. The room air group had lower Sp_{O_2} values between 2 and 10 min of life. Heart rates remained the same.	Titrating oxygen based on Sp_{O_2} readings to help minimize free radical formation
Dawson et al[21]	To describe changes in preductal Sp_{O_2} and heart rate in the first 10 min after birth in very preterm infants initially resuscitated with 100% oxygen or room air	Prospective observational study 126 infants less than 30 weeks' gestation	The 100% oxygen group reached higher Sp_{O_2} more quickly than the lower oxygen group. This may cause a quick onset of hyperoxia. The heart rates remained the same between the 2 groups	Utilizing pulse oximeters and Sp_{O_2} monitoring to provide optimal tissue oxygenation without exposing the infant to excessive free radical production

(*Continues*)

TABLE 1. Summary of Evidence-Based Literature and Links to Care in the Delivery Room, Continued

Author	Purpose	Design/Sample	Key Findings	Links to Care in Delivery Room
Ezaki et al[13]	To determine the effects of the level of inhaled oxygen during resuscitation on the levels of free radicals and antioxidative capacity in the blood of preterm infants	Blinded randomized controlled trial 44 infants less than 35 weeks' gestation born by cesarean delivery	Free radicals were higher in the 100% oxygen group ($P < .0001$) and antioxidant capacity was reduced in the high oxygen group ($P < .01$) as compared with the lower oxygen group	Oxidative stress can be reduced in the delivery room by lowering the inspired oxygen consecration through the guidance of pulse oximetry
Vento et al[20]	To determine if lower oxygen levels during resuscitation would cause less oxidative stress and inflammation and would reduce the need for oxygen supplementation and mechanical ventilation and/or the incidence of BPD	Randomized controlled trial 78 infants 28 weeks' gestation or less	The low oxygen group needed fewer days of oxygen supplementation, had fewer days of mechanical ventilation, and had a lower incidence of BPD at the time of discharge. The high oxygen group had increased markers for oxidative stress. These increased levels correlated significantly with the development of CLD	Spo_2 monitoring and oxygen titration when delivering oxygen in the delivery room can decrease oxidative stress, inflammation, and CLD
Rabi et al[3]	Compare 3 different oxygen titration strategies to determine which one was the best in maintaining Spo_2 ranges of 85%-92% during delivery room resuscitation	Blinded randomized controlled trial 106 infants 32 weeks' gestation or less	The moderate oxygen group spent most of the time in the target range than the high oxygen group. The low oxygen group had higher treatment failure rate	Spo_2 monitoring as a guide to titrate oxygen is an effective intervention to decreases the risk of overwhelming the tissues with free radicals

Abbreviations: BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; Fio_2, fraction of inspired oxygen; ROP, retinopathy of prematurity; Spo_2, oxygen saturation.

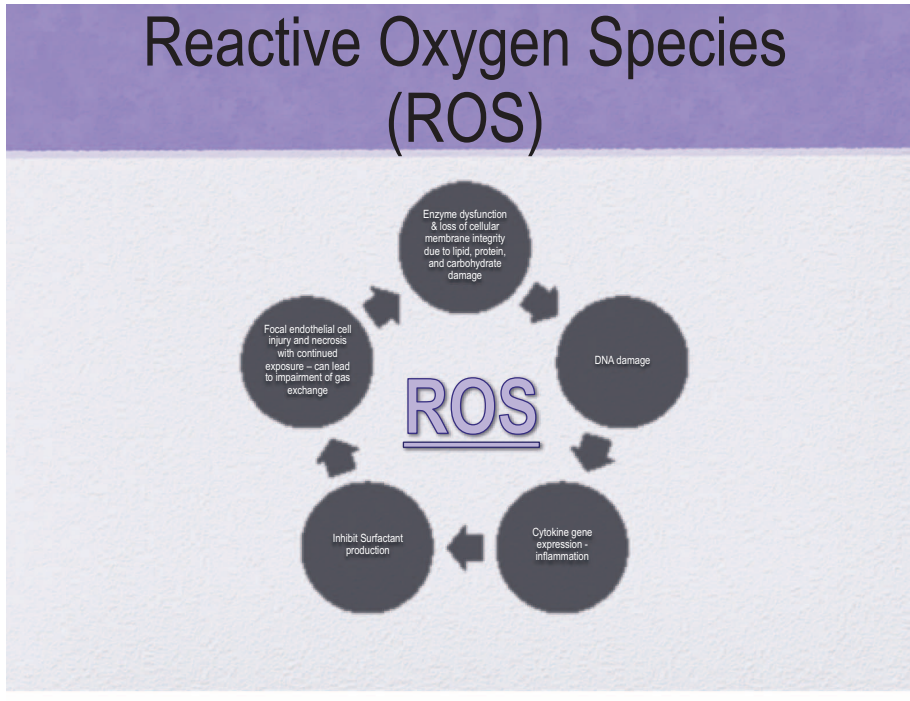
reduced to water. The superoxide anion is formed in aerobic cells and is produced by phagocytic cells in large quantities during oxidative stress.[8,11,28] The addition of an electron to the superoxide anion produces hydrogen peroxide. The superoxide anion and hydrogen peroxide can react to form the hydroxyl radical, which is the most reactive of the 3 free radicals.[7,8,11,28]

To minimize oxidative stress in the first critical minutes of life, it is important to understand normal fetal physiology and transition to extrauterine life. This knowledge can guide medical, nursing, and respiratory team in providing appropriate oxygenation while minimizing hyperoxemia. The partial pressure of oxygen in the fetus is 15 to 45 mm Hg in arterial blood, and the Spo_2 is 50%.[16,23] Fetal hemoglobin has an increased oxygen binding capacity with a left shift in the hemoglobin—oxygen dissociation curve. To compensate for this hypoxic environment, fetal hemoglobin is produced that can pick up oxygen from the maternal venous side and deliver it to tissues and organs, which allows for growth.[16] After birth, oxygen partial pressures in the arterial blood rise to 50 to 80 mm Hg with a mean Spo_2 of 59%, 68%, 82%, and 90% at 1, 2, 5, and 15 minutes if life, respectively.[16] Factors contributing to adequate cellular oxygenation include hemoglobin concentration, cardiac output, regional blood flow, and oxygen delivery to the cells.[7]

In addition, understanding how the administration of excessive oxygen during resuscitation can cause lung damage may assist the NICU team in becoming more cognizant of supplemental oxygen use in the delivery room. Lung injury caused by toxic ROS or oxygen free radicals is derived from sequential incomplete reduction of oxygen within the cells.[26] Oxygen free radicals can damage DNA, lipid, carbohydrate, and proteins, which can cause enzyme dysfunction and loss of cellular membrane integrity.[6,8,9,12,19,20] Reactive oxygen species can allow for enhanced expression of cytokine gene, which is involved in inflammation.[17,26] Reactive oxygen species can also inhibit the production of surfactant.[17,18]

Initial toxic oxygen concentrations can induce focal endothelial cell injury and cause necrosis with continued exposure. When pulmonary microvascular endothelial cells rapidly die after acute oxygen exposure, there is a disruption of the alveolar-capillary membrane and flooding of the alveoli, which can lead to impairment of gas exchange.[29] Recognition of the preterm infant's deficiency in the antioxidants SOD, catalase, and glutathione peroxidase should be a guiding factor in minimizing oxygen exposure, which can make this patient

FIGURE 1



A schematic representing the harmful effects of ROS at the tissue and cellular level.

population vulnerable to tissue damage.[5,9,10-12,14,16-20,22] Figure 1 displays a schematic of the harmful cellular effects of ROS.

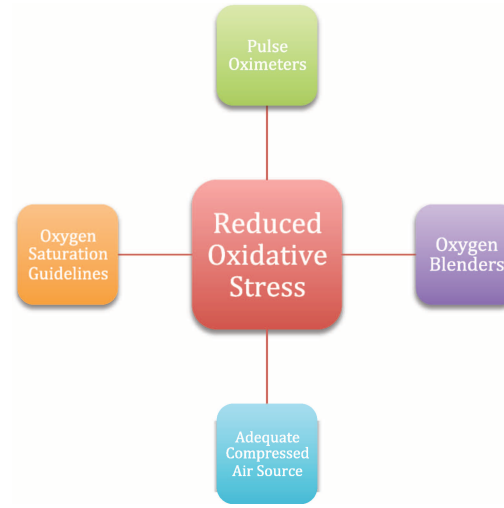
Adequate delivery of oxygen to the tissues is the most important goal when resuscitation is indicated in the delivery room.[12,17] Ideally, this should be done with the least amount of oxygen needed to deliver oxygen to the tissues to prevent toxicity and pathological processes.[17] Oxygen administration needs to be done in a way that promotes growth while minimizing associated risks.[5,12] Oxygen saturation values combined with assessment of heart rate can be highly effective predictors of effective neonatal resuscitation.[22] Starting resuscitation at an FIO_2 of 30% then titrating based on continued assessment of heart rate and SpO_2 can minimize the oxygen load to the neonate.[22] Part of the assessment in the delivery room should include maternal history and gestational age. As discussed previously, preterm infants are deficient in antioxidants, which can increase the oxidative stress to the infant.[12,17] A maternal history of abruption and conditions associated with fluid volume loss should be considered because volume support may be needed to assist in providing optimal cellular oxygenation.[17] By assessing maternal history, gestational age, SpO_2 levels, and heart rate, a synergistic balance of oxygen administered and sufficient tissue oxygenation could possibly be obtained.

Consideration of vaginal versus cesarean deliveries and the effect on oxygenation after cord clamping is 1 consideration during resuscitation in the delivery room. The SpO_2 does not reach preductal levels until 5 minutes after cord clamping in vaginal deliveries, and the SpO_2 reaching a preductal level of 90% may be delayed 2 or 3 minutes for those infants born by cesarean section.[16] Infants born by cesarean section may also have a decrease in antioxidant production.[19]

Diversity in gestational age is an important component in guiding resuscitation in the delivery room. Very preterm infants appear to be at greatest risk of oxidative damage due to oxygen exposure.[21] This is due in part to the immaturity of the antioxidant defense system.[5,9-12,14,16-20,22] In addition, treatment by sex effect could be a factor in SpO_2 monitoring. There could be an association of a better effect of avoiding high SpO_2 levels in females versus males.[6,7,30]

Education of staff and changes in clinical practice using evidence regarding avoidance of high SpO_2 levels and hyperoxia can improve outcomes, reduce the incidence of ROP and CLD, and reduce the length of stay in the NICU.[27] Adequate oxygenation during fetal to neonatal transition in the delivery room has essential components that require policy, organization, and financing, which include delivery room protocols, availability of pulse oximeters, oxygen blenders, and compressed air source at the baby.[17]

FIGURE 2



A representation of policies and guidelines that can be implemented in the delivery room to minimize oxidative stress caused by reactive oxygen species.

The most costly complication of very low-birthweight infants is CLD.[5] This should encourage facilities to develop policies and guidelines that promote the least amount of injury to the developing lung in the preterm infant. Figure 2 represents policies and guidelines that can be implemented to reduce oxidative stress in the delivery room.

Delivery room interventions may have a direct impact on immediate survival and long-term morbidity.[16] The NICU team must consider the quality of life of surviving extremely preterm infants and their families as oxidative stress has been shown to be associated with ROP, CLD, and NEC.[23] There is a moral responsibility among the neonatal resuscitation team of physicians, advanced practice nurses, staff nurses, and respiratory therapists in utilizing the best evidence-based practices to minimize oxygen toxicity.[31]

Collaboration and recognizing the need for titration of oxygen is a critical role of every member of the NICU team in the delivery room.[31] There should be consideration of factors such as knowledge, clinical experience, the use of research, intuition, individual factors, and organizational factors when developing evidence-based guidelines related to providing optimal oxygenation in the delivery room.[31] Reducing toxic oxygen states and minimizing the cellular response to oxidative stress in preterm infants exposed to hyperoxia are multidisciplinary responsibilities.[5] Respiratory therapy and nursing play a key role in managing SpO_2 target ranges on a daily basis based on unit policies.[31] Multidisciplinary teams are crucial in developing evidence-based

Summary of Recommendations for Practice and Research	
What we know:	• Exposing preterm infants to even brief amounts of oxygen can lead to oxidative stress • Oxidative stress occurs when there are more reactive oxygen species (oxygen free radicals) than the antioxidant system can handle • Oxidative stress is associated with several morbidities including retinopathy of prematurity, chronic lung disease, intraventricular hemorrhage, and periventricular leukomalacia
What needs to be studied:	• The effect of pulse oximetry use in the delivery room on long-term outcomes for preterm infants • Safe target range for preterm infant oxygenation in the delivery room • Effective resuscitation procedures for extremely preterm infants
What we can do today:	• Ensure delivery room providers are educated to resuscitation standards to minimize the tissue damaging side effects of oxygen

guidelines and policies to promote a safe and consistent approach to care given by all members of the NICU team.[31]

SUMMARY AND CONCLUSIONS

Oxygen administration to preterm infants in the delivery room is an intervention that requires knowledge of the current literature to minimize the tissue damaging side effects of oxygen. Minimizing oxidative stress in the first minutes after birth is a multidisciplinary task that requires collaboration among the health care personnel around each side of the resuscitation bed. Early research by Harling et al[26] did not find a clear benefit or disadvantage to resuscitating with a lower oxygen concentration.[26] Conversely, later research showed strong evidence for using pulse oximetry in the delivery room when administering oxygen during resuscitation to prevent a quick onset of hyperoxia, which could lead to an over abundance of free radicals in a patient population lacking antioxidant defenses.[3,13,20-23,27] Research has shown that starting at an intermediate concentration of oxygen and titrating based on Spo_2 monitoring may be an acceptable approach until further research is conducted.[3] Evaluation of Spo_2 with different delivered Fio_2 in preterm infants requires further research.[23] Future studies investigating if the use of pulse oximetry in the delivery room improves long-term outcomes for preterm infants and a safe target range for preterm infants in the delivery room are warranted.[21] Further research into the cellular response of hyperoxia in preterm infants and its relation to lung injury will be helpful to implement interventions in the delivery room that are harmful or useful to the preterm infant.[29] Long-term follow-up studies need to be done to change resuscitation procedures in extremely low gestational age infants.[16]

The NICU nurses, nurse practitioners, physicians, and respiratory therapists can spend a good majority of time in the delivery room, where interventions have the capability to set the tone for the clinical course in the NICU. The aforementioned literature review shows that understanding of cardiorespiratory transition in preterm infants and the sequelae that can result from over exposure to oxygen is crucial in caring for the preterm infant that requires resuscitation. There needs to be a call for action for every delivery room in developed countries to have pulse oximeters, oxygen blenders, and an adequate amount of compressed air available to every baby at the time of delivery to reduce oxidative stress and its associated disease processes.

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