Journal of Pulmonary & Respiratory Medicine

Aftab and Gerdes, J Pulmon Resp Med 2013, S13
DOI: 10.4172/2161-105X.S13-003

Review Article Open Access

Delivery Room Management of RDS

Saima Aftab[1]* and Jeffrey S Gerdes[2]

[1]*Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, USA*
[2]*Department of Pediatrics Chief Medical Officer, CHOP Care Network Children's Hospital of Philadelphia Perelman School of Medicine, University of Pennsylvania, USA*

Abstract

Respiratory Distress Syndrome RDS is a leading cause of short and long term morbidity and mortality in the preterm neonate. While the discovery and use of surfactant for RDS has improved neonatal survival as a whole, there are a variety of aspects of delivery room care that can improve outcomes further. In this article we will review evidence to optimize delivery room care of pre term neonate with RDS.

Keywords: Functional Residual Capacity (FRC); Continuous Positive Airway Pressure (CPAP); Respiratory Distress Syndrome (RDS); Broncho-Pulmonary Dysplasia (BPD); Extremely Low Birth Weight (ELBW) (an infant with birth weight less than 1000 grams); Very Low Birth Weight (VLBW) (an infant with birth weight less than 1500 grams); T Piece Resuscitator (TPR); Self Inflating Bag (SIB); Positive Inspiratory Pressure (PIP); Laryngeal Mask Airway (LMA); Fraction of Inspired Oxygen (FiO2), Minimally Invasive Surfactant Therapy (MIST); Intubation Surfactant Administration followed by Extubation (INSURE) to CPAP

Introduction

Respiratory Distress Syndrome or RDS is a clinical syndrome characterized by respiratory failure in a preterm neonate. An increasing understanding of lung immaturity came from the discovery of surfactant deficiency in infants who died of RDS, then known as hyaline membrane disease. The immature lung in RDS is deficient in surfactant and is prone to atelectasis, which in turn leads to lung inflammation and poor gas exchange. Before the introduction of mechanical ventilation and CPAP (Continuous Positive Airway Pressure) in the 1960's and 1970's, the only therapy for respiratory failure in the preterm newborn was oxygen and fluids [1].

Surfactant therapy for the treatment of RDS became available in the 1990s. Evidence from a series of surfactant studies indicated a decrease in mortality and morbidities, and led to its widespread acceptance of as standard of care for the prevention and treatment of RDS in preterm infants [2,3].

As the importance of establishing adequate lung volume or Functional Residual Capacity (FRC) early after birth was recognized, more interest in non-invasive methods of achieving this goal through early application of CPAP was investigated. CPAP was of particular interest as it was recognized that the process of intubation could lead to cardiovascular instability, and surfactant administration may itself lead to changes in cerebral blood flow. Those factors, coupled with data from animal studies linking volu-trauma and lung inflammation to future BPD (Broncho-Pulmonary Dysplasia), raised the importance of investigating non-invasive means of support.

Over the past 2 decades, widespread use of antenatal corticosteroids, regionalized care of the ELBW infant, progress in surfactant therapy and ventilatory support strategies, and improved team training in the delivery room have significantly improved survival, short-term complications, and long-term respiratory and neuro-developmental outcomes of the preterm neonate. In this article we will review the evidence for delivery room management of RDS, address controversies surrounding different therapies and explore ways to optimize lung recruitment, oxygen delivery and surfactant administration.

Pathophysiology of RDS

The anatomy and physiology of the preterm lung change dramatically between the periods of viability (23 weeks gestation) to 36 weeks gestation, when the risk of RDS reaches less than 5%. These changes include structural maturation, an increase in surfactant synthesis, and improved ability to clear fetal lung fluid and enhanced epithelial barrier function. These changes influence how surfactant treatment will interact with the lung and affect lung mechanics in the immediate newborn period, as well as how the improvements will change over time.

The fetal lung is filled with fluid secreted by the developing pulmonary epithelium. At birth effective transitioning from placental to pulmonary gas exchange requires removal of fluid from the lung. This process is initiated before birth, is augmented by labor and is completed several hours after independent breathing by the newborn. Both the birth-associated epinephrine surge and an increase in alveolar oxygen tension accelerate lung fluid resorption [4]. A combination of strong breathing effort and lung fluid resorption leads to establishment of lung volume or FRC. This allows spreading of endogenous surfactant further stabilizing lung inflation and facilitating gas exchange. At birth the pulmonary vascular resistance is high; after birth the pulmonary vascular resistance begins to drop, allowing for improved pulmonary blood flow, which in turn also improves oxygenation.

Respiratory Management for RDS in the Delivery Room: The Surfactant Question

Early vs. Late surfactant administration for the treatment of RDS

Initial randomized clinical trials of surfactant therapy in preterm neonates showed improvement in survival without chronic lung disease as well as reduction in the incidence of pneumothorax and air leak syndromes. While these early trials led to FDA approval and widespread adoption of surfactant therapy, ongoing research continued to fine-tune the details of surfactant treatment. One of the major areas of investigation has been the timing of surfactant dosing. Multiple

***Corresponding author**: Saima Aftab, MD, Assistant Professor of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, USA, E-mil: saima.aftabmd@gmail.com

Received March 16, 2013; **Accepted** June 13, 2013; **Published** June 17, 2013

Citation: Aftab S, Gerdes JS (2013) Delivery Room Management of RDS. J Pulmon Resp Med S13: 003. doi:10.4172/2161-105X.S13-003

randomized and quasi-randomized trials and the subsequent meta-analyses compared the outcomes for early (within the first two hours of life) compared to later treatment). The Cochrane Data base recently published a meta-analysis looking six large studies, which examined this question [5]. The meta-analyses demonstrated significant reductions in the risk of neonatal mortality (typical risk ratio (RR) 0.84; 95% Confidence Interval (CI) 0.74 to 0.95; typical Risk Difference (RD) -0.04; 95% CI -0.06 to -0.01; 6 studies; 3577 infants), chronic lung disease (typical RR 0.69; 95% CI 0.55 to 0.86; typical RD -0.04; 95% CI -0.06 to -0.01; 3 studies; 3041 infants), and chronic lung disease or death at 36 weeks (typical RR 0.83; 95% CI 0.75 to 0.91; typical RD -0.06; 95% CI -0.09 to -0.03; 3 studies; 3050 infants) associated with early treatment of intubated infants with RDS. Intubated infants randomized to early selective surfactant administration also demonstrated a decreased risk of acute lung injury including a decreased risk of pneumothorax (typical RR 0.69; 95% CI 0.59 to 0.82; typical RD -0.05; 95% CI -0.08 to -0.03; 5 studies; 3545 infants), pulmonary interstitial emphysema (typical RR 0.60; 95% CI 0.41 to 0.89; typical RD -0.06; 95% CI -0.10 to -0.02; 3 studies; 780 infants), and overall air leak syndromes (typical RR 0.61; 95% CI 0.48 to 0.78; typical RD -0.18; 95% CI -0.26 to -0.09; 2 studies; 463 infants). A trend toward risk reduction for broncho Pulmonary Dysplasia (BPD) or death at 28 days was also evident (typical RR 0.94; 95% CI 0.88 to 1.00; typical RD -0.04; 95% CI -0.07 to -0.00; 3 studies; 3039 infants). No differences in other complications of RDS or prematurity were noted [5].

Summary: Surfactant should be administered promptly when a preterm infant requires intubation and ventilator support for established RDS.

CPAP vs. Intubation/surfactant/ventilation as initial respiratory management in the delivery room

The early trials of surfactant treatment focused on babies who were intubated for respiratory support. As experience was gained with alternative non-invasive support strategies for RDS, the question was raised as to how to balance the proven benefits of surfactant therapy with the potential for reduced risk and improved outcomes with non-invasive support such as CPAP.

In the very beginning Aly et al. [6] performed a retrospective cohort study to evaluate the effect of an early nasal policy on outcomes of extremely low birth weight infants. They enrolled a total of 234 infants of which 83 infants, born before the CPAP policy, were intubated in the delivery room. 151, born after the policy, were placed on CPAP in the delivery room. A multivariate analysis for important factors showed that infants who were never intubated received fewer days of oxygen than infants who were briefly intubated in the delivery room and also had a lower death rate. Importantly in this study they found that a high percentage of infants who were tried on CPAP did not fail and there was no untoward effect of failing CPAP and requiring intubation [6].

Several randomized clinical trials have compared delivery room CPAP to mandatory intubation and ventilation. In the COIN trial (CPAP or Intubation at birth Trial), Morley et al. studied 610 infants born at 25-28 weeks gestational age. They found a non-statistically significant trend toward decreased rate of the primary outcome, death or BPD at 36 weeks corrected age, in the CPAP group. (33.9% vs. 38.9%, OR 0.80, 95% Cl 0.58, 1.12) [7]. There was, however, a significant increase in the rate of pneumothorax in the CPAP group [7].

In the SUPPORT trial (Surfactant Positive Pressure and Oxygen Randomized Trial) the NICHD Neonatal Research Network randomized 1316 infants born at 24-27 6/7 weeks to early CPAP in the delivery room or intubation and surfactant [8]. Again, the authors found a non-statistically significant trend toward decreased rate of the primary outcome, death or BPD at 36 weeks, in the CPAP group (47.8% vs. 51.0%, RR 0.95, 95% CI 0.85, 1.05). In this study, there were more infants in the CPAP arm alive and extubated at 7 days of life (55.3% vs. 48.8%, p=0.01) and fewer infants in the CPAP arm who received steroids for BPD (7.2% vs. 13.2%, p<0.001), without an increase in air leaks [8].

Further, a Vermont Oxford Network study randomized 648 infants born at 26-29 6/7 weeks gestation to intubation/prophylactic surfactant/mandatory ventilation, intubation/prophylactic surfactant/extubation to CPAP, or CPAP alone [9]. They also found a non-statistically significant trend towards less death or BPD at 36 weeks in the CPAP group when compared to the group who received mandatory ventilation in the delivery room (30.5% vs. 36.5%, OR 0.83, 95% CI 0.64, 1.09) [9]. When the 2358 infants from these studies are combined, there is a highly significant reduction in the odds of death or BPD at 36 weeks corrected age associated with the use of CPAP in the delivery room, odds ratio 0.80 (95% CI 0.68, 0.94).

The recently published trial of early CPAP by the South American Neocosur Network randomized infants to early CPAP or oxygen hood [10]. Surfactant was administered to both groups if the fraction of inspired oxygen concentration exceeded 35%. There was a reduction of the need for mechanical ventilation and the BPD/death rate tended to be lower in the early CPAP group. In addition to early CPAP, some recent trials have also tested an early surfactant strategy in addition to early CPAP. The trial by Verder et al. [11] initially managed infants on nasal CPAP immediately after birth and randomized infants to early surfactant administration or no early surfactant. This trial was stopped when an interim analysis showed that nasal CPAP with early surfactant administration significantly reduced the need for mechanical ventilation during the first week of life.

The CURPAP [12] and Colombian Network 4trials compared early CPAP with or without surfactant and reported that there was no difference in BPD rates between treatment strategies. However, there was a 9.1% lower BPD/death rate in the surfactant-treated infants in the Colombian trial [13] (53.9% in the CPAP surfactant group versus 62.8% in the CPAP only group) but it did not reach statistical significance.

Summary: CPAP started soon after birth is a strategy that appears to reduce BPD/death and is an alternative to the prophylactic or early surfactant approach. Infants treated with early CPAP instead of early surfactant are not at increased risk of adverse outcomes from delaying or eliminating surfactant administration. Thus, early CPAP is recommended based on the most recent evidence, with the caveat that babies who develop respiratory failure and require intubation and ventilator care receive surfactant treatment promptly after intubation.

Is there harm to intubating infants in the delivery room?

In an analysis of the Caffeine for Apnea of Prematurity trial, DeMauro and colleagues demonstrated a significant trend toward increased rates Of Broncho Pulmonary Dysplasia (BPD) in infants who were intubated in the delivery room, even when adjusting for multiple important prognostic factors [14].

The INSURE method vs. CPAP in initial respiratory management

An alternate approach to delivery room CPAP is the INSURE method, in which infants are intubated, receive surfactant, and then are immediately extubated to CPAP. The benefit of this approach would be

early administration of surfactant to any infant at risk for developing Respiratory Distress Syndrome (RDS). When compared to late, selective surfactant, early prophylactic surfactant reduces death or BPD in infants born <30 weeks and with established RDS [15]. Therefore, routine early prophylactic surfactant is an attractive approach. Unfortunately, this strategy has never been directly compared to CPAP alone in a randomized trial. Furthermore, the studies that established the superiority of early surfactant did not use CPAP support in their control arms and were performed in the era before routine use of antenatal steroids. The Vermont-Oxford Network study discussed above had INSURE and CPAP arms with equivalent results; however, these arms have not been directly compared to each other in the study's publications to date. Thus, the data in support of routine administration of delivery room CPAP is far stronger than the data in support of routine INSURE. It is important to emphasize that many of the subjects in the above trials who were randomized to delivery room CPAP did, eventually, require intubation and surfactant treatment.

The possible benefits of CPAP and INSURE was seen a recently published study comparing respiratory outcomes in two time epochs before and after introduction of early nasal CPAP and INSURE in the delivery room management of RDS. They observed a decrease in need for intubation, mechanical ventilation, oxygen therapy and mortality since the introduction of CPAP and INSURE. They also found a trend for lower BPD even though it did not reach statistical significance [16].

Summary: Hence we conclude that while delivery room CPAP is not expected to prevent all intubation events, there is no evidence of harm associated with starting CPAP in the delivery room. For those babies who require intubation for RDS INSURE may be a reasonable approach.

Use of surfactant when intubated for respiratory failure

For completeness, based on a 1999 Cochrane Review on early versus delayed selective surfactant treatment for RDS, which demonstrated reduced risk of death and/or CLD with early versus late surfactant in intubated infants, all ELBW infants who are intubated in the first 48 hours of life should receive at least one dose of surfactant [15].

Animal derived versus synthetic surfactants

A wide variety of surfactant preparations have been developed and tested. These include synthetic surfactants and surfactants derived from animal sources. Although clinical trials have demonstrated that both synthetic surfactants and natural surfactant preparations are effective, comparison in animal models has suggested that there may be greater efficacy of natural surfactant products, perhaps due to the protein content of natural surfactant [17]. Several randomized control trials have tried to compared safety and efficacy of natural versus synthetic surfactant. A meta-analysis of these randomized control trials published by Cochrane. The meta-analysis shows that the use of natural surfactant rather than synthetic surfactant results in a significant reduction in the risk of pneumothorax and the risk of mortality [18]. Natural surfactant extract is associated with a marginal increase in the risk of intraventricular hemorrhage (typical relative risk 1.09, 95% CI 1.00, 1.19; typical risk difference 0.03, 95% CI 0.00, 0.06), but no increase in grade 3 to 4 intraventricular hemorrhage (typical relative risk 1.08, 95% CI 0.92, 1.28; typical risk difference 0.01, 95% CI -0.01, 0.03). The meta-analyses support a marginal decrease in the risk of bronchopulmonary dysplasia or mortality associated with the use of natural surfactant preparations. No other relevant differences in outcome are noted. Both natural surfactant extracts and synthetic surfactant extracts are effective in the treatment and prevention of respiratory distress syndrome. Comparative trials demonstrate greater early improvement in the requirement for ventilator support, fewer pneumothoraces, and fewer deaths associated with natural surfactant extract treatment [18].

Summary: Natural surfactant extracts would seem to be the more desirable choice when compared to currently available synthetic surfactants.

MIST and other methods of surfactant administration

The beneficial effects of INSURE is likely due to surfactant administration, which led to interest in minimally invasive methods of administrating surfactant so the benefit could be delivered without the potential deleterious effects of intubation and mechanical ventilation. MIST would involve administering surfactant through a fine catheter directly into the trachea on a spontaneously breathing infant stabilized on nasal CPAP. This was investigated in the Avoidance of Mechanical Ventilation Trial that randomized 220 babies between 26-28 weeks gestational age BW<1500 g to either MIST or continuation of CPAP. This study not only demonstrated that this was feasible as the MIST was completed in the first attempt in 95% cases but it also showed that the babies undergoing MIST treatment had less need for mechanical ventilation and less need for oxygen at 28 days of life. MIST did not affect overall survival and no studies comparing MIST to INSURE are available [19]. Other techniques such as administering nebulized surfactant or nasopharyngeal surfactant or LMA (Laryngeal Mask Airway) surfactant administration has not been widely studied to determine if it is of any utility.

Methods of administering surfactant (ventilator vs hand bagging) Fractionated versus bolus dosing

There is some variation in the methods of surfactant administration such as bolus versus fractionating the dose, variations in infant positioning during administration interruption of mechanical ventilation and hand bagging versus administering through a side port adapter while remaining on mechanical ventilation. A randomized trial comparing surfactant administration as two or four fractionated aliquots did not find any difference in either fractional inspired oxygen, mean airway pressure, and arterial-alveolar ratio of partial pressure of oxygen at 72 hours of life, or in the incidences of air leaks, pulmonary interstitial emphysema, or death through 72 hours of life. There were no significant differences in the lowest heart rates recorded during administration of doses. The same study compared surfactant administration with hand bagging versus on mechanical ventilation and found that while giving the first dose there was less incidence of oxygen desaturation with mechanical ventilation than with hand bagging [20].

Another randomized trial compared surfactant administration in 2 aliquots followed by hand bagging versus single aliquot given through a side port adapter of the ETT over a minute while remaining on mechanical ventilation. The number of episodes of hypoxia and bradycardia were similar in both groups. A slight transient increase in PaCo2 was seen in the side hole group, however the efficacy of surfactant based on oxygenation and ventilation improvement was similar. There was also no difference in the incidence of IVH air leaks PDA BPD or survival in either group. This study showed no difference in the efficacy or side effect profile with surfactant administration either by hand bagging or mechanical ventilation [21]. While not formally studied in a detailed manner, maintaining FRC during surfactant administration is likely to benefit the RDS lung, since having adequate FRC is in itself a known benefit for treatment of RDS. The optimum tactic is to

maintain patient stability and FRC through use of a ventilator or t-piece resuscitator during surfactant administration.

Summary: Surfactant should be administered while maintaining FRC with a ventilator or T-piece resuscitator, and given in no more than two aliquots for each dose.

Respiratory Management for RDS in the Delivery Room: Questions Surrounding Non Invasive Respiratory Support

NIPPV

There has been substantial interest in the use of noninvasive ventilation for preterm infants, aiming to reduce invasive mechanical ventilation and associated complications [22]. The need for mechanical ventilation, especially early in life, is a major risk factor for the complex disorder of Broncho-Pulmonary Dysplasia (BPD) [23]. Nasal Continuous Positive Airway Pressure (NCPAP) is an initial respiratory support mode for many preterm infants with Respiratory Distress Syndrome (RDS), and this may have contributed to a significant decrease in the incidence of BPD at some centers. However, some infants fail NCPAP, and a newer noninvasive strategy that uses Nasal Intermittent Positive-Pressure Ventilation (NIPPV), with or without synchronization, has gained popularity as a mode of respiratory support for these infants [24]. A recent meta-analysis of several studies showed that among preterm infants with respiratory distress syndrome, NIPPV decreased the need for invasive ventilation within the first 72 hours of life compared with NCPAP. Trials are however still needed to assess whether NIPPV minimizes the occurrence of broncho-pulmonary dysplasia and other co-morbidities [25].

T piece resuscitator or a bag mask device

Effective positive pressure ventilation can be vital to neonatal resuscitation; in addition it is also important for uniform and effective surfactant distribution. A T piece resuscitator TPR or the traditional flow bag valve mask apparatus can deliver this positive pressure [26]. The TPR provides pressure controlled, flow delivered positive pressure ventilation. The Positive End Expiratory Pressure (PEEP) valve can be rotated to modify the PEEP provided, and occlusion of the valve by the operator delivers Peak Inspiratory Pressure (PIP). Its main purported advantages are the delivery of consistent pressures, the ability to adjust inspiratory time, and the control of PIP and PEEP [27]. There is a wide variability in the use of T piece resuscitator in neonatal resuscitations. There are several studies trying to compare the T piece resuscitator to the flow-inflating bag.

Dawson et al. [28] randomized infants less than 29 weeks' gestation to receive positive pressure ventilation with the Neopuff or the Self-Inflating Bag (SIB), and did not find a significant difference in mortality, need for endotracheal intubation or the need for respiratory support at 28 days. They also did not find a significant difference in oxygen saturation at 5 min (Neopuff 49%, SIB 59%) or heart rate at 5 min (Neopuff 135, SIB 138).

There are several mannequin studies comparing the T piece resuscitator to the self inflating or flow inflating bags on variables of ability to deliver target pressures, I time and Tidal volume variability and role of teaching for effectiveness of ventilation. TPR can provide PIPs that are closest to the target PIP with least variation when compared to users of the SIB and FIB. Similarly TPR users should be able to provide a PEEP that is closer the predetermined PEEP value [29]. Volu-trauma may potentially be less likely with the TPR as tidal volumes are smaller [30] and fewer variables in comparison to the SIB operators. TPR can provide a more consistent inspiratory time than SIB [29,31] and this does not depend on experience level [31].

TPR users should also be aware of certain limitations of the device. Resuscitation is a dynamic process where the resuscitator needs to adapt to the response or non-response of the newborn. TPR users are not as good at detecting changes in compliance as users of the Self or Flow Inflating bags. TPR users also need more time to change the inflating pressures during resuscitation, compared to users of the SIB or FIB. Mask leak is greater with the TPR than with other devices.

TPRs are also the most technically difficult of the 3 devices to prepare for use. Operators who do not frequently use the device, and are not receiving regular training in its setup, forget how to prepare the device for use. Instructors should be aware that increases in gas flow before, or during resuscitation could result in significant increases in pressures unless the operator adjusts the dials accordingly.

Until evidence of clinical benefit is available, we recommend that healthcare providers are appropriately and regularly trained in the use of whatever device being used in their clinical practice, and are aware of the particular limitations of that device.

Bubble CPAP versus variable flow CPAP

NCPAP can be administered via a constant flow system such as the traditional bubble CPAP device or a variable flow CPAP system. The safety and efficacy of Nasal Continuous Positive Airway Pressure (NCPAP) using devices with variable flow or bubble Continuous Positive Airway Pressure (CPAP) has been studied in randomized control trials has shown, no differences in CPAP failure, air leak syndromes and total CPAP time [32]. In babies previously intubated for RDS, extubation to bubble CPAP compared to a variable flow system was associated with a considerably shorter CPAP duration. The median duration of CPAP support was 50% shorter in the infants on bubble CPAP. Moreover, in the subset of infants who were ventilated for less than 14 days, the infants on bubble CPAP had a significantly lower extubation failure rate. There was no difference in the incidence of chronic lung disease or other complications between the 2 study groups [33]. Both constant and variable flow systems are safe and effective for CPAP delivery, bubble CPAP may offer an advantage for infants intubated <14 days in terms of less extubation failure, but this does not translate to less BPD. Bubble CPAP is inexpensive, easy to set up, and is of particular value in developing countries with scare resources. However as the level of CPAP is determined by the depth of insertion of the tubing in a water column, it requires close attention and substantial nursing care to avoid inadvertent excessive CPAP leading to barotrauma [34].

Respiratory Management for RDS in the Delivery Room: The O2 Question

Natural history of oxygen saturations after birth

In utero, fetal oxygen saturation is approximately 60%. Full-term babies may take more than 10 minutes for oxygen saturations to be above 90%, though the majority reach >90% by 5-8 minutes [35]. Oxygen saturations measured post-ductally increase at a slower rate than those measured pre-ductally [36]. There is a slower rise in oxygen saturations after cesarean section delivery, compared to vaginal delivery [37]. Lastly, preterm neonates have a slower rise in oxygen saturations than term infants, and values overall remain lower. For example, at 5 minutes of life and without intervention, the 50th percentile of saturations in infants <32 weeks is 86% and the 10th percentile is 72% [38] compared to 92% and 75%, respectively, in the term baby. Despite the fact that

normal transition is associated with a slow rise in oxygen saturation, it is common delivery room practice to monitor oxygen saturation in very low birth weight infants and to provide supplemental oxygen within the first minutes of life, to increase the oxygen saturation. The safety of this practice has never been demonstrated and several studies suggest harm.

Safety of room air resuscitation in term infants and larger preterm infants

Recent studies have evaluated the safety of room air, rather than supplemental oxygen, for infant resuscitation. When neonates >1000 grams were resuscitated with room air, there was no difference in mortality, hypoxic ischemic encephalopathy, length of resuscitation (time to first cry was shorter), or "treatment failure" [39]. There was no difference in growth, attainment of developmental milestones, hearing, cerebral palsy or mental retardation at 18 or 24 months of age [40]. A meta-analysis of 6 randomized and 4 quasi-randomized trials showed a significant reduction in mortality for infants resuscitated in RA vs. 100% oxygen (randomized: RR 0.32(0.12-0.84), quasi-randomized: RR 0.74(0.57-0.95), all: RR 0.69(0.54-0.88) [41].

Harm associated with resuscitation with 100% oxygen

Furthermore, some studies suggest harm associated with 100% oxygen resuscitation. When asphyxiated term neonates were resuscitated with 100% oxygen or room air, the infants resuscitated with room air had shorter time to first cry and return of regular respiratory pattern, shorter length of resuscitation, and lower markers of oxidative stress at 48 hours and 28 days of life [42]. Furthermore, there are two case-control studies demonstrating a higher incidence of childhood cancer in infants exposed to as little as 3 minutes of oxygen in the delivery room when compared to those never exposed to oxygen [43,44].

Studies of high vs. low starting oxygen levels in preterm infants (including ELBWs)

Four studies have evaluated the differences between high and low oxygen resuscitation for preterm infants. Wang and colleagues found infants failed to reach the goal saturations of 70% at 3 minutes and 85 at 5 minutes of life when they were started on room air. When compared to the group resuscitated with 100% oxygen, there were no differences in heart rate at any time in the first 10 minutes of life or in any of the secondary outcomes [45].

In the ROAR study, investigators studied 106 infants less than 32 weeks gestation. The infants were assigned to one of three groups: 1) start at 100% and do not titrate, 2) start at 100% and titrate down based on oxygen saturation, or 3) start at 21% and titrate up based on SpO_2. A significantly higher percentage of infants in the groups with the titrating protocols spent time in the target saturation range of 85-92% [46].

Escrig and colleagues conducted a randomized trial of 42 infants with birth weight less than 1000 grams. Resuscitation was started at 30% in one group and 90% in the other. FiO_2 was adjusted by 10% every 60 to 90 seconds to keep the heart rate above 100 and achieve a saturation goal of 70% at 5 minutes and 85% at 10 minutes. The low oxygen group ultimately had a stepwise increase in inspired oxygen to 45%, while the high oxygen group had a reduction in inspired oxygen to 45%. Both groups had saturations of about 85% at 5 to 7 minutes of life and they found no difference in mortality [47].

Finally, Vento et al. [48] continued the Escrig study for an additional year, to evaluate rates of Broncho Pulmonary Dysplasia (BPD), defined as oxygen requirement at 36 weeks post conceptual age, based on initial oxygen exposure. They found that the low oxygen group had lower rates of BPD, fewer days of oxygen supplementation and mechanical ventilation, and lower markers of oxidative stress [48].

Based on this evidence, we arrived at the following recommendations for the management of oxygen in the delivery room.

1. Place pulse oximetry probe on infant's right hand, the preductal location.
2. Start at 30% oxygen and titrate by 10% every minute to achieve target saturation.
3. Goal oxygen saturation is:

a. 70% by 5 minutes of life

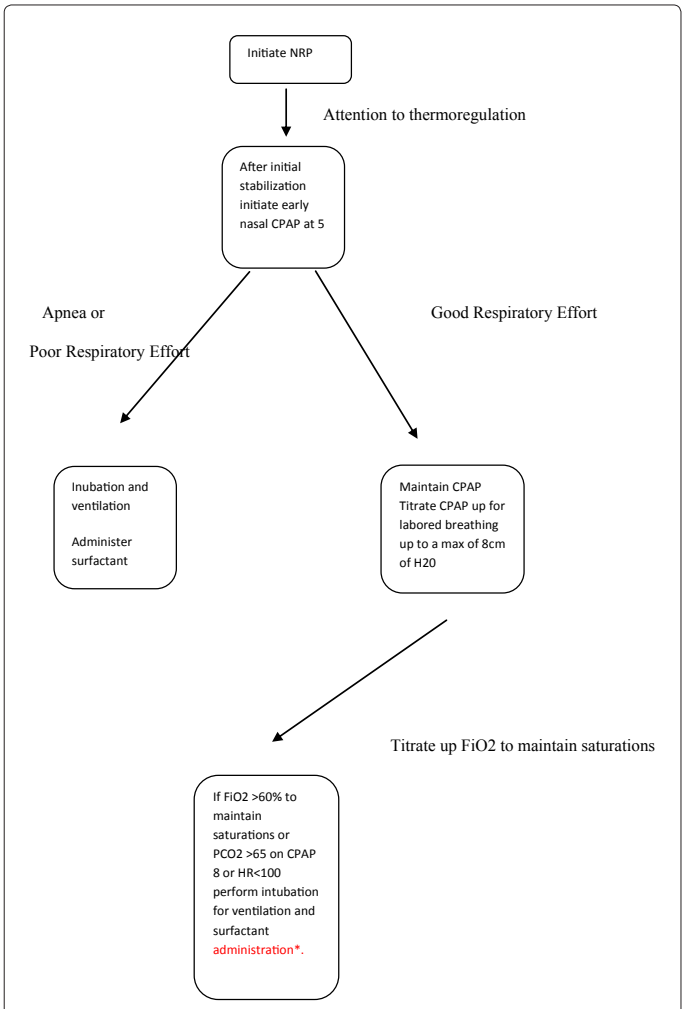
b. 85-92% by 10 minutes of life

If the infant has prolonged bradycardia (HR<100), may increase immediately to 100% oxygen (Figure 1).

Non-invasive respiratory support is the first line therapy for all ELBW infants:

Establish a team leader, usually a neonatology fellow or attending.

Airway - experienced personnel, usually a senior nurse practitioner, fellow or attending



*Consider INSURE intubation with surfactant administration following by early extubation to CPAP

Figure 1: Recommendations for DR Management of RDS.

Routine gentle bulb suction and stimulation

Immediately initiate CPAP 5cm and titrate (max 8 cm) to reduce work of breathing and O_2 requirement

Use CPAP interface that allows the infant to be placed on the ventilator in the resuscitation room if possible during umbilical line insertion.

Intubation criteria:

0. HR<100 or hemodynamic instability

ι. PCO2>65

ιι. FiO2>60% to maintain saturations per oxygen guidelines

ιιι. Apnea or severe distress

ιϖ. Established RDS with rising oxygen requirement in the first 24 hours of life

When in doubt, the INSURE (intubate, give surfactant, extubate to CPAP) approach seems to be an acceptable alternative until more data from randomized trials are available.

For infants on CPAP, start caffeine immediately upon admission to neonatal intensive care unit

All ELBW infants intubated in the first 48 hours of life should receive at least one dose of surfactant promptly after intubation.

Continue to foster a culture that supports use of non-invasive respiratory support in the delivery room and in the unit

Pay attention to other aspects of care of the newborn such as thermoregulation and establishing access.

Conclusion

Improvement in perinatal care has resulted in improved respiratory outcomes in newborns with RDS. Combining years of neonatology experience with current day evidence will help ensure that we optimize management of RDS. It is essential to have excellent teamwork and communication in the delivery room. It is extremely important to establish early lung recruitment and CPAP appears to be a reasonable initial approach. Once it is evident that a baby is failing CPAP the baby should be intubated for prompt surfactant administration. Although good studies are lacking INSURE may be considered provided the baby has good respiratory effort and has a reasonable expectation to be able to tolerate extubation to CPAP. Novel methods of surfactant administration via LMA and MIST seem to have promise but more studies will need to be done to determine their safety and efficacy. Close attention should be paid to the oxygen saturations in the delivery room. FiO2 should be carefully titrated to keep saturations within target range.

References

1. Kamath BD, Macguire ER, McClure EM, Goldenberg RL, Jobe AH (2011) Neonatal mortality from respiratory distress syndrome: lessons for low-resource countries. Pediatrics 127: 1139-1146.
2. Soll RF (2000) Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev : CD000511.
3. Soll RF (2003) Synthetic surfactant for respiratory distress syndrome in preterm infants Cochrane Database Syst Rev 2: CD001149.
4. Carlton DP (2011) Regulation of Liquid Secretion and Absorption by the Fetal and Neonatal Lung: Fetal and Neonatal Physiology Polin, Fox and Abman (4thedn), Elsevier Saunders, Philadelphia.
5. Bahadue FL, Soll R (2012) Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev 11: CD001456.
6. Aly H, Massaro AN, Patel K, El-Mohandes AA (2005) Is it safer to intubate premature infants in the delivery room? Pediatrics 115: 1660-1665.
7. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, et al. (2008) Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 358: 700-708.
8. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, et al. (2010) Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 362: 1970-1979.
9. Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, et al. (2011) Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics 128: e1069-e1076.
10. Tapia JL, Urzua S, Bancalari A, Meritano J, Torres G, et al. (2012) Randomized trial of early bubble continuous positive airway pressure for very low birth weight infants. J Pediatr 161: 75-80.
11. Verder H, Albertsen P, Ebbesen F, Greisen G, Robertson B, et al. (1999) Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 103: E24.
12. Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, et al. (2010) Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics 125: e1402-e1409.
13. Rojas MA, Lozano JM, Rojas MX, Laughon M, Bose CL, et al. (2009) Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. Pediatrics 123: 137-142.
14. DeMauro SB, Roberts RS, Davis P, Alvaro R, Bairam A, et al. (2011) Impact of delivery room resuscitation on outcomes up to 18 months in very low birth weight infants. J Pediatr 159: 546-550.
15. Soll RF, Morley CJ (2001) Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev: CD000510.
16. Flor-de-Lima F, Rocha G, Guimarães H (2012) Impact of changes in perinatal care on neonatal respiratory outcome and survival of preterm newborns: an overview of 15 years. Crit Care Res Pract 2012: 643246.
17. Tooley WH, Clements JA, Muramatsu K, Brown CL, Schlueter MA (1987) Lung function in prematurely delivered rabbits treated with a synthetic surfactant. Am Rev Respir Dis 136: 651-656.
18. Soll RF, Blanco F (2011) Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2: CD000144.
19. Göpel W, Kribs A, Ziegler A, Laux R, Hoehn T, et al. (2011) Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet 378: 1627-1634.
20. Zola EM, Gunkel JH, Chan RK, Lim MO, Knox I, et al. (1993) Comparison of three dosing procedures for administration of bovine surfactant to neonates with respiratory distress syndrome. J Pediatr 122: 453-459.
21. Valls-i-Soler A, López-Heredia J, Fernández-Ruanova MB, Gastiasoro E (1997) A simplified surfactant dosing procedure in respiratory distress syndrome: the "side-hole" randomized study. Spanish Surfactant Collaborative Group. Acta Paediatr 86: 747-751.
22. Ramanathan R (2010) Nasal respiratory support through the nares: its time has come. J Perinatol 30 Suppl: S67-72.
23. Jobe AH (2011) The new bronchopulmonary dysplasia. Curr Opin Pediatr 23: 167-172.
24. Bhandari V (2010) Nasal intermittent positive pressure ventilation in the newborn: review of literature and evidence-based guidelines. J Perinatol 30: 505-512.
25. Meneses J, Bhandari V, Alves JG (2012) Nasal intermittent positive-pressure ventilation vs nasal continuous positive airway pressure for preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. Arch Pediatr Adolesc Med 166: 372-376.
26. Hawkes CP, Ryan CA, Dempsey EM (2012) Comparison of the T-piece resuscitator with other neonatal manual ventilation devices: a qualitative review. Resuscitation 83: 797-802.

27. Kattwinkel J, Denson S, Zaichkin J (2006) Textbook of neonatal resuscitation (5thedn), American Academy of Pediatrics.

28. Dawson JA, Schmölzer GM, Kamlin CO, Te Pas AB, O'Donnell CP, et al. (2011) Oxygenation with T-piece versus self-inflating bag for ventilation of extremely preterm infants at birth: a randomized controlled trial. J Pediatr 158: 912-918.

29. Hussey SG, Ryan CA, Murphy BP (2004) Comparison of three manual ventilation devices using an intubated mannequin. Arch Dis Child Fetal Neonatal Ed 89: F490-F493.

30. Roehr CC, Kelm M, Fischer HS, Bührer C, Schmalisch G, et al. (2010) Manual ventilation devices in neonatal resuscitation: tidal volume and positive pressure-provision. Resuscitation 81: 202-205.

31. Roehr CC, Kelm M, Proquitté H, Schmalisch G (2010) Equipment and operator training denote manual ventilation performance in neonatal resuscitation. Am J Perinatol 27: 753-758.

32. Yagui AC, Vale LA, Haddad LB, Prado C, Rossi FS, et al. (2011) Bubble CPAP versus CPAP with variable flow in newborns with respiratory distress: a randomized controlled trial. J Pediatr (Rio J) 87: 499-504.

33. Gupta S, Sinha SK, Tin W, Donn SM (2009) A randomized controlled trial of post-extubation bubble continuous positive airway pressure versus Infant Flow Driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. J Pediatr 154: 645-650.

34. Gunlemez A, Isken T (2008) Bubble CPAP must be used with care to avoid harm. Arch Dis Child Fetal Neonatal Ed 93: F170-F171.

35. Kamlin CO, O'Donnell CP, Davis PG, Morley CJ (2006) Oxygen saturation in healthy infants immediately after birth. J Pediatr 148: 585-589.

36. Toth B, Becker A, Seelbach-Göbel B (2002) Oxygen saturation in healthy newborn infants immediately after birth measured by pulse oximetry. Arch Gynecol Obstet 266: 105-107.

37. Rabi Y, Yee W, Chen SY, Singhal N (2006) Oxygen saturation trends immediately after birth. J Pediatr 148: 590-594.

38. Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, et al. (2010) Defining the reference range for oxygen saturation for infants after birth. Pediatrics 125: e1340-e1347.

39. Saugstad OD (1998) Resuscitation with room-air or oxygen supplementation. Clin Perinatol 25: 741-756.

40. Saugstad OD, Ramji S, Irani SF, El-Meneza S, Hernandez EA, et al. (2003) Resuscitation of newborn infants with 21% or 100% oxygen: follow-up at 18 to 24 months. Pediatrics 112: 296-300.

41. Saugstad OD, Ramji S, Soll RF, Vento M (2008) Resuscitation of newborn infants with 21% or 100% oxygen: an updated systematic review and meta-analysis. Neonatology 94: 176-182.

42. Vento M, Asensi M, Sastre J, García-Sala F, Pallardó FV, et al. (2001) Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics 107: 642-647.

43. Naumburg E, Bellocco R, Cnattingius S, Jonzon A, Ekbom A (2002) Supplementary oxygen and risk of childhood lymphatic leukaemia. Acta Paediatr 91: 1328-1333.

44. Spector LG, Klebanoff MA, Feusner JH, Georgieff MK, Ross JA (2005) Childhood cancer following neonatal oxygen supplementation. J Pediatr 147: 27-31.

45. Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, et al. (2008) Resuscitation of preterm neonates by using room air or 100% oxygen. Pediatrics 121: 1083-1089.

46. Rabi Y, Singhal N, Nettel-Aguirre A (2011) Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study. Pediatrics 128: e374-e381.

47. Escrig R, Arruza L, Izquierdo I, Villar G, Sáenz P, et al. (2008) Achievement of targeted saturation values in extremely low gestational age neonates resuscitated with low or high oxygen concentrations: a prospective, randomized trial. Pediatrics 121: 875-881.

48. Vento M, Moro M, Escrig R, Arruza L, Villar G, et al. (2009) Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. Pediatrics 124: e439-e449.

This article was originally published in a special issue, **Controversies in the Management of Respiratory Distress Syndrome in Premature Neonates** handled by Editor(s). Dr. Alan Fujii, Boston University, USA