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# Treatment for Respiratory Distress in Premature Infants

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By Teresa Pacelli

## **Abstract**

There are many different opposing studies about respiratory distress and how it affects premature infants as well as adults. The main focus is on how infants can be treated of acute respiratory distress syndrome or ARDS, which is more common when they are born prematurely. This analytical review is designed to capture all the past and present data in order to present both sides of controversy in the different treatments to treat respiratory distress in premature infants. The data finds that inhaled nitric oxide (iNO) is one of the main treatments for respiratory distress and has had a lot of controversy over the years. Most of the research points to the usefulness of iNO in different doses, although it is controversial as to the right dose amount. There are also a few other treatment possibilities that still need further research. iNO is useful as a treatment, and could be a temporary treatment before other treatments can be administered. However, it still has different risks involved especially when dealing with infants.

## **Introduction and Background**

Acute Respiratory Distress Syndrome can be common in newborns as well as adults causing different breathing complications. It's a common and devastating clinical syndrome that affects both medical and surgical patients. It is a lung condition where fluid collects in the lungs air sacs, which deprives the body and other organs of oxygen. It was first called the adult respiratory distress syndrome, but now the acute respiratory distress syndrome, since it does occur in children. In 1988, an expanded definition was

proposed that quantified the physiologic respiratory impairment through the use of a four-point lung-injury scoring system that was based on the level of positive end-expiratory pressure, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, the static lung compliance, and the degree of infiltration evident on chest radiographs. Other factors included in the assessment were the inciting clinical disorder and the presence or absence of nonpulmonary organ dysfunction (Ware et al. 2000).

Although the lung-injury scoring system has been widely used to quantify the severity of lung injury in both clinical research and clinical trials, it cannot be used to predict the outcome during the first 24 to 72 hours after the onset of the acute respiratory distress syndrome and thus has limited clinical usefulness. When the scoring system is used four to seven days after the onset of the syndrome, scores of 2.5 or higher may be predictive of a complicated course with the need for prolonged mechanical ventilation (Ware et al. 2000). The purpose of this paper is to analyze all the different techniques and treatments for premature newborns with respiratory failure and/or respiratory distress syndrome, as well as the underlying controversy of these treatments or ways to prevent the disease itself.

## **How to Help Premature Babies with Respiratory Distress**

### **Possible Treatments:**

A study was done regarding the value of lung ultrasound as early diagnostic tools in Respiratory Distress Syndrome, or RDS. The study found that there was a significant correlation between ultrasound and radiographic assessments of RDS. It found out that chest ultrasounds cannot replace standard chest x-rays in diagnosing potential causes of

neonatal respiratory failure because of its tendency to over estimate RDS, but are useful at excluding RDS as a screening method for diagnosis. It found that chest ultrasounds are important to consider as a screening method. This is important in describing the way RDS can be diagnosed in infants as well as premature babies, because they have to be properly diagnosed before treatment can occur. These conclusions were made by using 40 preterm neonatal patients that were admitted to the intensive care unit in Madina national hospital that were suffering with RDS. All the patients were subject to a full maternal history as well as laboratory investigations that were performed including blood count, blood sugar, chest x-rays and chest ultrasounds (Abdelsadek et al. 2015).

Another study assessed the utility and compared the outcomes of infants that did not use nasal biphasic positive airway pressure (n-BiPAP). They used infants with RDS that were admitted to the hospital between 2002-2010 and treated them with n-BiPAP treatment protocol. The study found that increasing use of n-BiPAP was associated with reduced morbidity in infants with RDS, so this may be an ethically sound and sustainable way of generating knowledge about the disease as well as its treatment along with other treatments (Solevag et al. 2015).

There are different treatments that can be given, that include low doses of nitric oxide. There was a study done that shows that the most important difference between their trial and previous studies is that they used a low dose of inhaled nitric oxide for a limited amount of time (a maximum of 96 hours). Other trials have used higher doses (80 ppm) for longer periods (as long as two weeks). By limiting the duration of treatment, they hoped to avoid delaying extracorporeal membrane oxygenation beyond the point at which its efficacy might be reduced. The data, combined with the results of previous

studies, suggest that this approach is effective. In the neonatal inhaled nitric oxide (iNO) study, neonates who did not have a response to 20 ppm of nitric oxide had a response to 80 ppm. The median duration of successful treatment in this study was 44 hours, and all but two neonates were weaned from nitric oxide by 96 hours (Clark et al. 2000).

A study done to assess the association between serum levels of 25-hydroxyvitamin D (25OHD) and the outcomes in preterm infants. They found a high prevalence of low 25OHD, and they also found an association between the status of vitamin D and acute respiratory morbidity in preterm infants after birth. They did this by measuring the serum in mothers and their infants within 24 hours after birth. This study can possibly lead to the idea that maybe a higher prevalence of vitamin D could help against respiratory distress and can be similar to how vitamin A supplements are used and then just different vitamin supplements in general. The study demonstrated a significant association between vitamin D status and acute respiratory morbidity in infants after birth. Maintaining adequate maternal vitamin D levels during pregnancy is important in optimizing an infant's vitamin D status at birth (Onwuneme et al. 2015).

Other research discusses how premature infants are at an increased risk of wheezing with association to different respiratory problems like respiratory syncytial virus (RSV) and rhinovirus infections. The study found that wheezing lower respiratory diseases or WLRD risk had no increased evidence following routine vaccinations of premature infants. The study found no evidence of increased risk of medically attended WLRD among premature infants following routine vaccinations. The risk of WLRD among premature infants that were non-fragile appeared to be reduced for a few weeks

after vaccinations. If there is the possibility of vaccinating infants so that they are at less of a risk of respiratory problems this could be a great advantage (Mullooly et al. 2011). Something also that's important to distinguish is the area of infants and adults and their differing affects to the distress. Treatments for infants vs. adults due to their differing affects to the distress is also an important area of research, because there are differences where it can be useful in adults and maybe not in infants.

A study demonstrates the feasibility of administering low-dose glucocorticoid therapy and measuring clinically relevant outcomes in pediatric acute respiratory distress syndrome. Changes in oxygenation and/or ventilation are consistent with early acute respiratory distress syndrome pathophysiology and results of similar clinical trials in adults. Consistent with earlier adult studies and reported cases in pediatric patients with ARDS they found higher Pao<sub>2</sub> /Fio<sub>2</sub> ratios (of oxygen) in the steroid group on days 8 and 9 (after 7 days of steroid infusion) and fewer patients required supplemental oxygen at PICU transfer. Pao<sub>2</sub> is the partial pressure of arterial oxygen and Fio<sub>2</sub> is the fraction of inspired oxygen. They speculated that steroid therapy may have reduced lung inflammation, and they launched efforts to examine inflammatory markers in these patients. Unlike the adult clinical trials or pediatric cases reported. Higher plateau pressures occurred in the steroid group at enrollment, suggesting poorer compliance than placebo group, but lower Pao<sub>2</sub> values on days 2 and 3 and higher pH on day 2 in the steroid group could indicate a decrease in dead space ventilation (Drago et al. 2015). There are treatments of inhaled nitric oxide therapies that are also useful in helping infants/premature babies with ARDS and respiratory problems, and these other possible

treatments are also candidates to be used along with iNO possibly where iNO is a rescue intervention to buy more time for other treatment to be done.

Use of iNO and other supplement treatments:

In preterm infants, inhaled nitric oxide (iNO) improves gas exchange in infants with respiratory distress syndrome and persistent pulmonary hypertension. In animal models, iNO reduces lung inflammation and oxidant stress that cause acute lung injury in preterm infants. iNO maintains surfactant activity and improves lung structure in experimental models of bronchopulmonary dysplasia (BPD). BPD is a form of chronic lung disease that affects newborns, mostly premature ones. It results from damage to the lungs that are caused by mechanical ventilation and/or long-term oxygen. Despite favorable preclinical studies, the effects of iNO for the prevention of human BPD have been variable. In 2 randomized control studies, iNO therapy improved pulmonary outcomes and survival in preterm newborns born. The separate effects of iNO therapy and vitamin A supplementation have been studied in animal models and human studies, but in no previous study have authors examined the effects of the combination of both of these therapies in preterm newborns at risk for BPD. Ongoing postnatal deficiency of vitamin A in very low birth weight preterm infants may promote chronic lung disease by impairing lung healing, contributing to the loss of cilia, increasing epithelial cell metaplasia and susceptibility to infection, and decreasing the number of alveoli in lung parenchyma. Although exact mechanisms by which iNO reduces risk of BPD are uncertain, nitric oxide decreases neutrophil adhesion in microcirculation, which may attenuate the inflammatory cascade that contributes to lung injury and BPD in the



preterm infant (Gadhia et al. 2014). The mechanisms of this therapy are important to discuss in order to better understand how nitric oxide affects the bodies of these infants.

## **Inhaled Nitric Oxide (iNO)**

### **Mechanisms:**

Mechanisms through which inhaled nitric oxide therapy might provide neuroprotection in the premature newborn are uncertain. A possible explanation is that inhaled nitric oxide modulates circulating cells (including neutrophils, monocytes, and platelets) as they transit the pulmonary circulation; the down-regulation of lung-derived cytokines that is induced by inhaled nitric oxide may also reduce the injury of distant organs. Another possible mechanism may relate to the distal delivery to the central nervous system of nitric oxide or nitric oxide-related metabolites through the systemic circulation through pathways mediated by red cells or proteins (Kinsella et al. 2006). There is controversy over the topic and whether or not iNO is useful and what other vasodilator can be used, some found it useful while others did not (Adhikari et al. 2014).

### **Current Research and Controversy of iNO:**

The response of dosage shows that the lowest dose is the more effective treatment. There was a study done on a multicenter randomized controlled trial of inhaled nitric oxide for pediatric acute respiratory distress syndrome. It found that iNO led to a significant reduction in the duration of mechanical ventilation. Previous studies of iNO in pediatric ARDS were either designed with or allowed for a crossover to iNO, precluding an analysis on the impact of iNO on outcomes in pediatric ARDS. The most common precipitating cause for ARDS in adults is sepsis, but in children it is pneumonia, and

there are likely differences in the organisms responsible for these diseases (Bronicki et al. 2014).

The main finding is that iNO does not reduce hospital mortality in patients with Acute Respiratory Distress Syndrome or ARDS, regardless of the severity of hypoxemia. In the study the effects of iNO did not differ between more hypoxemic and less hypoxemic patients. Most of the trials did not measure oxygenation index, an alternative measure of hypoxemia that incorporates mean airway pressure as a marker of the intensity of mechanical ventilation. The number of patients in the severe ARDS subgroup was relatively small, limiting the statistical power of our analysis to detect true differences in mortality between subgroups. Clinicians can argue that the dose used in included studies was insufficient to improve gas exchange in the most severely hypoxemic patients, who would be expected to be at highest risk from imminent death due to hypoxemia.

However, the trials included in this review suggest otherwise. Of the trials that titrated NO to achieve improved oxygenation (50–53), the lowest and most effective dose was 5–10 ppm in three trials and ~13 ppm in the fourth trial. These findings are consistent with a detailed dose-response study that found that the average increase in of the oxygen level in the blood that is breathed was maximal at 5 ppm (Adhikari et al. 2014).

The study done was able to show a clear dose as a response relationship for this very preterm group of infants. Considering the results of this study within the context of other similar studies they advised the use of the lowest effective dose possible in any clinical application. Where no pulmonary vasodilator response is seen at any dose but

there is a clinical decision to continue with inhaled nitric oxide, iNO. Analysis of the infant characteristics at trial entry between responders and non-responders showed only that male infants were more likely to show a clinical response than female infants. Given the small study size this difference, although statistically significant, may still represent a chance finding. The high patient variance indicated that there was great variability in how different infants responded to the dosing but little variability within a single infant. Statistical analysis of the results indicated no convincing evidence of a dose response effect once the effect of period and infant variability was taken into account. Coordinators of future randomized trials of iNO in this high-risk population should continue to consider the value of further dose—response studies to add to these data for a technique that must still be viewed as experimental in the preterm infant (Ahluwalia et al. 2006). New research should really focus on finding out more about these treatments and what dosage is really useful.

### **Future research of iNO**

There is other research that should be conducted and what still needs clarification to know more about treatments. The processes underlying preterm birth are poorly understood. The incidence and the underlying causes of preterm birth are known to vary geographically and temporally. Environmental exposures, such as pollution and tobacco smoke, and individual behavioral differences also contribute. Interference with the fetus's natural environment during critical windows of development causes many different affects. The processes underlying preterm birth challenge the developmental plasticity of the lungs and airways. Common antecedents of preterm birth such as

inflammation, maternal smoking, metabolic derangement, hypoxia, and growth restriction have well-recognized adverse effects on lung maturation and structure, T cell polarization and development, and airway reactivity. Such alterations can differentially affect susceptibility of the lungs to injurious exposures that commonly follow preterm birth, including sepsis, respiratory infections, mechanical ventilation, and hyperoxia. Preterm birth furthermore augments the association of several of these risk factors, such as antenatal inflammation and smoke exposure, with childhood wheezing. Genetic influences and gene–environment interactions are furthermore likely to play a role, and the link between preterm birth and asthma has been suggested to at least partially reflect a common genetic background (Been et al. 2014).

Pulmonary vasodilator study done on lambs to test reversing of hypoxic pulmonary vasoconstriction as another treatment possibility. This study demonstrates that iNO can act as a selective local pulmonary vasodilator without causing systemic vasodilation. iNO reversed the pulmonary hypertension caused by infusing the stable endoperoxide analogue U46619 without decreasing systemic arterial pressure. Eight Suffolk lambs weighing 25-35 kg underwent a sterile thoracotomy to place a left atrial line, a tracheostomy, and a femoral artery line under general endotracheal anesthesia with halothane and oxygen 3 days before the study. After this recovery period, the lambs underwent sterile placement of a 7F thermodilution pulmonary artery monitoring catheter (Edwards Laboratories, Santa Ana, Calif.) through a jugular vein under local anesthesia. At all dose levels, iNO produced a prompt reduction of the pulmonary hypertension caused by U46619 infusion. They believe rapid combination with hemoglobin in red blood cells inactivates iNO, restricting iNO vasodilation to vessels in the lung and

preventing systemic vasodilation (Frotell et al. 1991). Along with all this future research that needs should be conducted and is being conducted now because some of this research is from the early 90s, the different risks for treatment of iNO should also be taken into consideration.

## **Risks of iNO**

Pediatric intensivists all over the world are challenged in predicting which child with pediatric acute respiratory distress syndrome (PARDS) is destined to die. Identifying a child with a high likelihood of mortality is important in counseling families, in guiding therapeutic decisions, and in designing studies intended to evaluate the efficacy of novel therapies. In their recent publication, the acute lung injury consensus conference (PALICC) reviewed mortality rates in PARDS from 1992 to 2013 in multiple observational and epidemiologic studies and discovered a range of 10–50% in those inclusive of over 100 children (Anas 2016).

The risks involved in using inhaled nitric oxide with fears of damage to cells in ventilated preterm infants. There have been fears that iNO could increase free radical damage to cells. This is a particular concern in ventilated preterm infants already under considerable oxidative stress and with compromised anti-oxidant defenses. A randomized controlled trial of treatment with iNO therapy and/or intravenous dexamethasone in preterm infants at risk of developing chronic lung disease (CLD) was performed. This pilot study was designed to look for evidence of increased lipid peroxidation after iNO. Urine and breath samples were collected before treatment commenced and 6, 24, 48 and 72 hours after beginning therapy in treated and control subjects. Urinary

malondialdehyde (uMDA) was measured by HPLC and breath pentane by GC with thermal desorption. Gestation and birth weight were similar in both groups. There were no statistical differences in outcome measures between treated and non-treated infants. The pre-treatment pentane exhalation rate was similar in the two groups studied. Study ultimately found the difference in the risk to be insignificant and iNO does not increase lipid peroxidation, which involves cell damage that is caused by free radicals (Drury et al. 1998). Different risks do not just affect babies when they are born but can also affect them long term as well.

### **Later in Life Impacts and Controversy with iNO**

Long term effects of iNO:

In animal models, iNO decreases baseline airway resistance and may increase the rate of alveolarization. To date of the study, only 2 studies have reported respiratory outcomes of preterm infants treated with iNO. In a telephone survey that included 456 infants in the Nitric Oxide Chronic Lung Disease (NOCLD) study group, the use of bronchodilators, inhaled steroids, systemic steroids, diuretics, and supplemental oxygen during the first year of life was less in the iNO-treated group. There are no significant differences in the frequency of wheezing or the rate of rehospitalization. In the Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide multicenter trial, follow-up at 1 year of age showed no difference in maximal expiratory flow at functional residual capacity, wheezing, readmission rate, or use of respiratory medications (Kumar 2014).

In recent years new and interesting effects of iNO, in addition to improving oxygenation, have been observed in animals and people. These effects may modify

pathophysiological events in the lung during respiratory distress. Early administration of iNO has been shown to be anti-inflammatory, to be anti-proliferative on vascular smooth muscle cells, and to promote normal lung development. It is now known that iNO after pulmonary absorption can be transported outside the lung and used in redox-based signaling and some extrapulmonary effects may be undesirable, such as reversible changes in kidney function (Lindwall et al. 2005).

Effects of early school age of iNO:

At 2 years of age, iNO-treated premature infants in our study had approximately half the risk of cognitive impairment exhibited by the placebo-treated group, since there was a control (placebo) and then a group that was administered nitric oxide. This marked difference in cognitive impairment was not apparent at school age indicates that factors outside the neonatal period, such as the home environment and socioeconomic status, become increasingly important as infants acquire more complex repertoires of skills and behaviors. To assess whether beneficial effects of iNO treatment during prematurity persisted to early school age, first they compared the incidences of chronic morbidities between groups. There were no significant differences between groups in the percentage of children having one or no chronic morbidities. Significantly fewer iNO-treated infants had multiple chronic morbidities or were dependent on technology compared with placebo-treated infants and because the presence of multiple chronic morbidities or dependence on technology strongly reduces the likelihood of school readiness, these data suggest that, by decreasing the total morbidity burden, iNO may decrease the number of premature children requiring additional societal resources (Patrianakos-Hoobler et al.

2011)

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A relook at a study done over 20 years ago on iNO and vasodilation:

The study published in 1993 was one of the first to provide evidence for selective pulmonary vasodilation produced by breathing NO in adult ARDS patients. It offered the advantage of lowering the elevated pulmonary artery pressures, improving arterial oxygenation, and protecting the right ventricle from failure without reducing systemic arterial resistance or pressure. iNO proved superior to classical intravenous vasodilators in ARDS, since breathing NO reduced and did not increase the pulmonary right-to-left shunt fraction. Researchers studying ARDS never demonstrated an improved outcome with iNO treatment. However, breathing iNO is still used to buy time to institute other therapies in severely hypoxemic ARDS. Maybe now that low volume ventilation has become standard therapy in ARDS, a trial of breathing iNO to improve the outcome of ARDS patients should be considered. Future research may yield synergistic beneficial effects in terms of outcome between iNO and other advanced ARDS treatment modules (Rossaint et al. 2014).

Another study found this to be ineffective though through other testing in iNO. iNO as rescue therapy for the very ill ventilated preterm infant does not appear to be effective and may increase the risk of severe interventricular hemorrhage (IVH) (Barrington et al. 2010). So, in the current era of protective mechanical ventilation, some clinicians employ iNO breathing for a period of 24–48 hours as a rescue intervention for severely hypoxemic patients to buy time and allow other therapies like Extracorporeal Membrane Oxygenation (ECMO) or prone positioning to improve the patients' pulmonary gas exchange (Rossaint et al. 2014).



## The current controversy of different treatment options:

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The study found that low-dose inhaled nitric oxide reduced the incidence of bronchopulmonary dysplasia in infants with a birth weight of 1000 g or more. There was no significant reduction in the incidence of bronchopulmonary dysplasia among infants with lower birth weights. Various factors other than inhaled nitric oxide, including the stage of lung development at birth, influence the need for supplemental oxygen at 36 weeks of postmenstrual age. The multifactorial nature of lung injury and repair at the extremes of prematurity may limit the efficacy of any single intervention, and the targeting of 36 weeks of postmenstrual age for an evaluation of the pulmonary reparative capacity of newborns with extremely low birth weights may not be an adequate end point (Kinsella et al. 2006).

Another study investigates antenatal steroid treatment and postnatal surfactant replacement therapy and was completed by reviewing 70 complete autopsies. Then the lung tissues were examined and graded. They were put in control and experimental groups with the treatment being the mother getting the surfactant and the steroid. The study found that there was a significant reduction in the severe hyaline membrane that was associated with combined surfactant and antenatal steroid therapy. However the cause for the similar incidence of the selected histopathological findings in the treatment groups and the control could be linked to oxygen toxicity due to insufficient antioxidant capacity in premature infants and barotrauma from mechanical ventilation. While the study found all this information it could lead to controversy since the findings were not found to be significant in the study, however they did not find this surprising because they excluded patients who were successfully treated and discharged so it is hard to relate

these findings to treatment regimens, possibly a better study would invite the discharged patients back to get tested on (Teksam et al. 2009). This is another possible treatment instead of iNO that could be administered as inhaled steroids, but hopefully the use of iNO would reduce the need for using this kind of treatment.

## **Conclusion**

This research topic interested me significantly because I was born ten weeks prematurely, and it seems that there is still a lot of research that needs to be done on the affects of premature birth and possible treatments that can help. This is a good step in that direction even though there is still some controversy on the topic of iNO being a good treatment method, as it having side affects in the long run possibly. Having to get a cesarean section or just a natural premature birth can cause problems to the baby, as well as the mother having been sick, so it an important field to continue to study and learn more about.

Different research options should be looked into more as well such as the vaccines and supplemental vitamins that can help prevent respiratory distress in infants. Some studies are contradicting, although also important to note the span of time from the 90s until now that all of these studies have occurred in, now there is better medicine and babies are born earlier and earlier but with risk of more complications. There is still uncertainty of mechanisms of treatments, and with lots of trial and error, may only be useful in severe cases otherwise would not want to risk using some treatments. There are still risks with iNO and these treatments, especially since the mechanism is still not fully understood or how much of the dosage of the treatment is necessarily effective in every case.

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*Academic Festival, Event 7 [2017]*

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