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Strategies to minimize lung injury in extremely low birth weight infants

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Abstract

Objective: To review the main causes of new bronchopulmonary dysplasia and the strategies utilized to decrease its incidence in extremely low birth weight infants.

Sources of data: For this review a MEDLINE search from 1966 to October 2004, the Cochrane Database, abstracts from the Society for Pediatric Research and recent meetings on the topic were used.

Summary of the findings: The survival of extremely low birth weight infants has increased significantly due to improvement in both scientific knowledge and technology. This improvement in survival has therefore resulted in an increased incidence of bronchopulmonary dysplasia. The characteristics of bronchopulmonary dysplasia in extremely low birth weight infants, the so called "new" bronchopulmonary dysplasia are quite different from the classic bronchopulmonary dysplasia described by Northway. This new bronchopulmonary dysplasia has a multifactorial etiology, which includes volutrauma, atelectrauma, oxygen toxicity and lung inflammation. Therapy such as prenatal corticosteroids, exogenous surfactant, nasal continuous positive airway pressure, new mechanical ventilation modalities and gentle ventilation have been used in attempts to decrease lung injury severity.

Conclusions: In order to prevent lung injury in extremely low birth weight infants, it is necessary to minimize several factors that induce bronchopulmonary dysplasia and to utilize less aggressive therapeutic strategies. In addition to the current therapy used to decrease lung injury, knowledge of these causative factors may create new therapies that may be fundamental in improving the clinical outcomes of premature infants.

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Introduction

With technological advances and new knowledge and therapeutic strategies such as the use of antenatal corticosteroids, exogenous surfactant and advances in mechanical ventilation, premature babies are surviving more than ever. With this increased survival of extremely premature infants, the incidence of bronchopulmonary dysplasia (BPD) remains high.[1-4] Among babies born weighing 500-1,000 g, the incidence of BPD is around 43%.[4] In the neonatal intensive care unit at the University of Miami's Jackson Memorial Hospital, however, the incidence of BPD is significantly lower, affecting around 23% of extremely premature infants.[5]

The clinical presentation and pathophysiology of BPD in the extremely premature infant is different from the classic form that was described by Northway, and it is this entity that has been named "new" bronchopulmonary dysplasia. New BPD is defined as oxygen dependency at the 36th week of postmenstrual age (with oxygen dependency $\geq$ 28 days).

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The histopathology of the lung damage is different because extremely premature infants' lungs are at a less advanced stage of development. The degree to which the lung has developed at 24-26 weeks is very different to the degree of development at 30-32 weeks' gestational age. At 24 weeks the lung is still at the canalicular development stage, which lasts from 16 to 26 weeks' gestational age and is characterized by type 2 pneumocyte differentiation, by the start of development of pulmonary circulation and the fine saccules which will eventually form the alveoli. At this stage the lung is beginning to be viable for gaseous exchange. At 30 weeks the lung is in the saccular stage. This period develops from 26-28 to 32-36 weeks' gestational age and is characterized by the increase in size of these saccules and the reduction in interstitial space. The alveolar stage lasts from 32-36 weeks' gestational age until more or less 2 years of life.[6] Thus, premature delivery and the start of breathing interrupt the normal development of the alveoli and pulmonary vasculature of these infants.

The classic form of BPD described by Northway et al.[7] occurs after mechanical ventilation has been used because of severe respiratory failure due to respiratory distress syndrome (RDS). At that time, newborn babies were subjected to more aggressive mechanical ventilation and it was barotrauma and oxygen toxicity that were primarily responsible for BPD. Classic BPD, during the initial phase, is characterized by interstitial and alveolar edema which progress to an inflammatory process with significant fibrosis. In contrast, new BPD, observed in extremely premature infants, is the result of a number of different factors such as pulmonary immaturity and the inefficiency of the musculature and the thorax, causing the need for longer periods on the respirator, which in turn increases the chances of the airways being colonized by bacteria, initiating an inflammatory reaction. With the new BPD, injuries present with less fibrosis, there is more uniform aeration and, primarily, a reduction in the number of alveoli and capillaries[1,5,8] (Table 1).

Table 1 - Characteristics of the classic and new bronchopulmonary dysplasia

Classic bronchopulmonary dysplasia
Severe respiratory distress syndrome
Severe respiratory failure
High mortality rate
Severe pulmonary hypertension
Aggressive mechanical ventilation (barotrauma/volutrauma)
X-ray with hyperdistension and emphysema
Alveolar atelectasis contrasting with alveolar hyperdistension
Reduction in the internal alveolar surface
Severe epithelium airways injuries (hyperplasia and metaplasia)
Airways smooth muscle hyperplasia
Significant fibrosis
Vascular lesions
New bronchopulmonary dysplasia
Moderate respiratory distress syndrome
Mild to moderate respiratory failure
Lower mortality rate
Gentle mechanical ventilation, prolonged ventilation
X-ray with less hyperdistension and emphysema
More uniform aeration
Reduction in the number of alveoli, which became bigger, simplified structure (hyperplasia and metaplasia, reduced acinar complexity)
Less severe epithelium airways injuries
Variable airways smooth muscle hyperplasia
Variable interstitial fibrosis
Less severe vascular lesions
Reduced number of capillaries, which are dysmorphic

Causes of lung damage

Lung damage can be caused by prenatal factors or postnatal occurrences.

Prenatal factors

It has been observed that premature infants exposed to chorioamnionitis during the neonatal period present elevated concentrations of inflammatory mediators and that this condition can lead to pulmonary maturation and, as a result, a reduced BPD incidence. However, if these premature infants develop RDS and require mechanical ventilation, the incidence of BPD increases significantly.[9-11]

Postnatal factors

Inadequate alveolar stability

Premature infants' lungs are generally deficient in surfactant, which triggers alveolar atelectasis and reduction in pulmonary compliance. The use of mechanical ventilation for recruitment of atelectatic alveoli can cause lung damage.[12]

Volutrauma/barotrauma

Studies have demonstrated that mechanical ventilation with large tidal volume increases the number of neutrophils and cytokines in the lungs and also the permeability of the capillary membrane, leading to pulmonary edema. These inflammatory injuries can be associated with BPD.[13-15] Large tidal volumes provoke hyperdistension of the alveoli, causing lung damage. Volutrauma associated with the tendency towards alveolar atelectasis and surfactant deficiency increases the chance of injury. In such cases the lungs are not ventilated symmetrically. For example, if the lungs are being ventilated with a tidal volume of 10 ml/kg and just one third is expanding, then this fraction is in fact being ventilated with the equivalent of a 20-30 ml/kg volume. Nowadays barotrauma is less common although some services still insist on using higher pressures during mechanical ventilation, causing this type of lesion.

Oxygen toxicity

Experimental studies demonstrate that mechanical ventilation and oxygen can interfere with the alveolar and vascular development of premature animals.[16-18] In premature infants, the activity of antioxidant enzymes, such as superoxide dismutase, catalase and peroxidase, is relatively deficient, making them more vulnerable to oxygen toxicity.[19] Oxygen metabolites can saturate the antioxidant system, inhibit the synthesis of proteins and of DNA and reduce surfactant synthesis. Prolonged exposure to high concentrations of oxygen can lead to inflammation and diffuse alveolar injury. Premature infants who have been exposed to high oxygen concentrations in order to maintain high saturation levels, exhibit more persistent lung damage.[20]

Inflammatory reaction

Recently published data have demonstrated that inflammatory mediators, such as TNF-alpha and interleukins, increase during mechanical ventilation, particularly when large tidal volumes are employed.[13,14,21-25] Naik et al. observed that starting premature lambs on mechanical ventilation triggered an increase in inflammatory mediators, suggesting that a few mechanical ventilation cycles are enough to cause lung damage.[15] Sepsis and patent ductus arteriosus can also set off an inflammatory reaction and are associated with an increased incidence of BPD.[26,27]

Strategies for minimizing lung damage in the extremely premature infant

As can be observed, the factors that trigger lung damage in premature neonates are multiple. Measures for avoiding these injuries should start during the prenatal period and, if premature delivery cannot be avoided, continue through the neonatal period.

Prenatal care

Prenatal monitoring is critical to early diagnosis and treatment of possible maternal infections which can lead to chorioamnionitis. As has already been covered, chorioamnionitis, when associated with RDS, is one of the risk factors for BPD.

When premature delivery is inevitable, antenatal corticosteroid is of fundamental importance. Corticosteroid administered before birth stimulates pulmonary maturation, increasing surfactant production and accelerating the development of alveolar and capillary structures, which reduces the severity of hyaline membrane disease (HMD) and the need for mechanical ventilation.[28,29]

Postnatal care

The care given to premature newborns during the first hours of life can be of fundamental importance to minimizing acute lung damage and its complications, such as BPD.

The introduction of new technologies and the development of modern respirators have provided different ventilation and monitoring modalities, which, together with antenatal corticosteroid and exogenous surfactant, have significantly improved the prognosis of these patients.[30-32]

Surfactant therapy

The surfactant deficient lungs of premature neonates are highly susceptible to lung injury and significant inflammatory reactions can be triggered.[33] The function of surfactant is to recruit alveoli and prevent atelectasis. Treatment with surfactant reduces the need for ventilatory support in order to maintain adequate gaseous exchange, thereby reducing the risk of volutrauma and oxygen toxicity.

Its use is further associated with an increase in functional residual capacity (FRC), an improved ventilation-perfusion coefficient and reduced intrapulmonary shunt.[34] Clinical studies demonstrate that surfactant reduces the occurrence of RDS, pneumothorax, and the severity of chronic lung disease.[34-41]

The great debate around surfactant is on when the first dose should be administered. Controlled, randomized studies show that surfactant replacement therapy is effective both when used prophylactically, soon after birth to prevent RDS, and when administered selectively, i.e. only when the patient exhibits signs of the disease. In a review for Cochrane including 2,800 premature subjects, Soll & Morley observed a lower incidence of pneumothorax and reduced mortality rates among those newborn babies who had been treated prophylactically with natural surfactant, when compared with those who had only been given surfactant after a diagnosis of RDS had been established.[41] Despite these studies, many centers still prefer to use surfactant only when there are signs of RDS, based on the reasoning that not all premature infants need exogenous surfactant, particularly not those who have received antenatal corticosteroid.

With respect of whether to use natural or synthetic surfactant, Soll & Blanco concluded, having reviewed several different studies, that both natural and synthetic surfactants are effective for the prevention and treatment of RDS. However, the natural surfactant provokes a faster reduction in the need for mechanical ventilation, a lower number of pneumothorax cases and a more accentuated reduction in mortality rate, compared with the synthetic form.[42] Clinical and experimental research is being performed with new synthetic surfactants, such as rSP-C (Venticute), KL4 (Surfaxin), HL 10 (Rotterdam) and SP-C33 (Stockholm).

Non-invasive ventilatory support

In continuous positive airway pressure (CPAP), continuous pressure is applied throughout the entire respiratory cycle to prevent the alveoli from collapsing and thus permit more homogenous breathing. In addition to recruiting alveoli and increasing pulmonary volume, CPAP reduces thoracic distortions and stabilizes the chest, while also reducing the incidence of obstructive apnea and increasing surfactant excretion.[43] As a less invasive method than mechanical ventilation, CPAP is being studied as a possible early treatment, even before extremely premature infants leave the delivery room.

Studies show that employing CPAP reduces the duration and need for intubation, which reduces the risk of BPD. In the United States, during the eighties, a retrospective study showed that the incidence of BPD was significantly reduced in the neonatal ICU at the University of Columbia, in New York. At this unit, premature infants born weighing 700-1,500 g and showing signs of respiratory failure were treated with nasal CPAP soon after birth.[44] This study did, however, suffer certain criticisms because it was not randomized and also because, in addition to the use of CPAP, elevated $PaCO_2$ levels were tolerated. Later, Verder et al. observed that the need for mechanical ventilation was reduced significantly if newborn babies received exogenous surfactant and were quickly extubated for CPAP, when compared with those that were put on CPAP later or did not receive surfactant and were just put on CPAP.[45] Sandri et al. demonstrated, in a randomized study of premature babies born at 28-31 weeks' gestational age and treated with prophylactic CPAP 30 minutes after birth, that there were no reductions in the need for surfactant or mechanical ventilation when compared with premature babies treated with therapeutic CPAP, i.e. when CPAP was started if the child required FiO_2 above 0.4 in order to maintain oxygen saturation above 93% for more than 30 minutes.[46] Since existing studies of early CPAP remain controversial and a definitive practice has not yet been fixed, the National Institutes of Health (NIH) in the United States is conducting a new study to try to better define early CPAP use. In this project CPAP will be started in the delivery room for newborn babies whose gestational ages are less than 28 weeks.

Parameters for CPAP should be set according to the needs of each patient. Positive end expiratory pressure (PEEP should be around 4-6 cmH_2O, $PaCO_2$ should be tolerated at 45-65 mmHg and oxygen set to maintain PaO_2 between 50-70 mmHg). In order to reduce the incidence of lung damage in addition to tolerate more conservative parameters, CPAP should always be used with the airflow humidified and heated and there should also be continuous monitoring of the adequate functioning of the system.

Invasive ventilatory support

Conventional and synchronized mechanical ventilation

The objective of mechanical ventilation during the initial phases of RDS is to maintain adequate oxygenation and ventilation, using gentle ventilation in order to minimize ventilator induced lung injuries (VILI). One of the major debates currently is whether premature newborn babies should be intubated electively or only when there are signs of respiratory failure. Drew et al. presented a randomized study and showed that selectively intubated neonates born weighing less than 1,500 g and given respiratory support after birth exhibited better progress and survival than those intubated only when necessary.[47] Other studies, however, demonstrate disadvantages with elective intubation; O'Brodovich showed that acute lung damage induced by respirator soon after birth can lead to chronic lung disease.[33] Naik et al. found that just a few cycles of mechanical ventilation were enough to trigger an inflammatory reaction in premature lambs.[15]

Several different strategies have been employed to minimize lung injury once the newborn is already on mechanical ventilation. Conventional mechanical ventilation, pressure-limited and time-cycled, has been hugely employed in neonatology for several decades. This ventilation modality is easily managed and accessible to all neonatal ICUs, but if the patient does not synchronize

with the respirator, there is a risk of lung damage. Nowadays, synchronized ventilation modalities such as synchronized intermittent mandatory ventilation (SIMV) or assisted/controlled (A/C), have proven their efficacy and ability to provide lower support parameters on the respirator. The respirators used for this type of ventilation have microprocessor-controlled units coupled to them which detect the start of spontaneous breathing by means of flow or pressure variation and trigger a mechanical breath. Synchronized ventilation allows the newborn to participate in the work of respiration, thus reducing the respirator parameters. The advantages of synchronized ventilation over conventional ventilation are: increased tidal volume at each breath, providing better alveolar ventilation and allowing positive inspiratory pressure (PIP) to be reduced; better oxygenation; reduced risk of barotrauma; reduced variation in cerebral blood flow; earlier weaning off ventilation and increased patient comfort as the newborn does not have to "fight" against the respirator. A more detailed description of new modalities for neonatal mechanical ventilation can be found in a specialized review article.[48]

The studies cited above have shown that it does not take long for ventilation to cause lung injury to premature newborns – just a few cycles can trigger an inflammatory reaction. Therefore, gentle ventilation is of fundamental importance to reducing the incidence of these injuries. At the neonatal ICU at the University of Miami's Jackson Memorial Hospital, the incidence rate of BPD is one of the lowest of any of the ICUs that participate in the NIH Neonatal Network, despite opting for early intubation and mechanical ventilation. This is probably the result of using the gentle ventilation strategy with low tidal volume and a short inspiratory period, with controlled oxygen supply and higher levels of $PaCO_2$ being tolerated.

In order to achieve gentle ventilation with premature newborns it is necessary to know what parameters are being used nowadays:

Tidal volume and inspiratory pressure – one of the most important factors during mechanical ventilation is to use reduced tidal volume. In premature infants with lung disease, FRC is reduced and some parts of the lungs have collapsed. The ideal tidal volume would be that which can open these collapsed areas without causing volutrauma. When ventilation takes place with the ideal tidal volume, reduced intrapulmonary shunt is observed together with a reduction in the effect of elevated pulmonary volume on cardiac output, in addition to improved oxygenation. The most modern respirators calculate tidal volume and the oldest ones can be coupled to pneumotachographs which determine tidal volume. The tidal volume of a spontaneous breath should be the guide for the tidal volume to be administered in mechanical ventilation. Currently the option of choice is to use tidal volumes of around 4-6 ml/kg, particularly in extremely premature infants. Normally, at the start of mechanical ventilation, the PIP level is set first, based on the patient's needs, and tidal volume is calculated. The use of elevated pressures is contra-indicated because of the elevated risk of causing barotrauma. In general, initial PIP is 18-20 cmH_2O in order to achieve a tidal volume of 4-6 ml/kg in premature infants with HMD. The PIP is then modified according to the results of arterial blood gases, which should be performed frequently, although in general the maximum PIP used to ventilate extremely premature infants should not exceed 20 cmH_2O.

Expiratory pressure and inspiratory time – in addition to tidal volume and PIP, studies have shown that mechanical ventilation with zero or too high PEEP and long inspiratory times can cause lung injury. Positive end expiratory pressure should be set in accordance with each disease. Newborn babies with HMD require PEEP at 4-6 cmH_2O, although PEEP above 4 cmH_2O should be avoided in newborns exhibiting left-right shunt, arterial hypotension, low pulmonary compliance or hypoventilation with elevated $PaCO_2$ and for premature infants born weighing less than 1,000 g. The use of long inspiratory times is associated with a greater incidence of pneumothorax. Currently, short inspiratory times are being used during the neonatal period, around 0.3-0.4 seconds, and 0.4 seconds should not be exceeded except for short periods to recruit collapsed alveoli.

Oxygen supply – hyperoxia during the neonatal period can be as deleterious as hypoxia. Tin et al. demonstrated that newborn babies who received O_2 supplementation in order to maintain saturation at 88-98% developed more chronic lung disease than did those who received O_2 to maintain saturation at 70-90%.[49] The STOP-ROP research group (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity) showed that newborn babies who had received O_2 supplementation to maintain saturation at 96-99% presented more pneumonia and a greater incidence of chronic lung disease than did those whose saturation was maintained at 89-94%.[20] Oxygen has detrimental effects such as pulmonary toxicity, increasing interstitial liquid, followed by fibrosis and metaplasia of the bronchial epithelium. Therefore, oxygen supply should be limited to the minimum needed to maintain PaO_2 at 50-70 mmHg and saturation at the pulse oximeter at 90-94%. The benefits of using antioxidants for reducing lung damage are not yet established.

Permissive hypercapnia – recently higher levels of $PaCO_2$ have been tolerated, thus allowing more gentle ventilation in an attempt to minimize lung damage induced by high respirator parameter settings. Studies show that permissive hypercapnia is protective in terms of lung damage and hypoxic-ischemic brain damage.[50-52] Retrospective studies suggest that BPD occurs more often among newborn babies with hypocapnia. Kraybell et al. observed that extremely premature infants with $PaCO_2$ below 40 mmHg presented a relative risk of 1.45 for BPD development, compared with newborn babies with $PaCO_2$ above 50 mmHg.[53] Garland et al. observed that patients with $PaCO_2$ lower than 30 mmHg during the first 24 hours of life, before treatment with surfactant, had a much higher risk of developing BPD, compared with those presenting $PaCO_2$ above 40 mmHg.[54] In a randomized and controlled study of the NIH Neonatal Network, including 220 babies born at 501-1,000 g, it was

observed that the group put on a permissive hypercapnia regimen ($PaCO_2$ > 52 mmHg) required less ventilatory support at 36 weeks' corrected age than did a control group ($PaCO_2$ < 48 mmHg) (1 *versus* 16% for the control group), but no reduction was observed in BPD. Unfortunately, the study was stopped early because of complications related to the use of corticosteroids.[55] However, Woodgate & Davies, in a review produced for Cochrane in 2001, did not observe any advantage from permissive hypercapnia and hypoventilation compared with conventional ventilation.[56] Despite the need for further studies, the current tendency is to accept a moderately elevated level of $PaCO_2$, of 45-65 mmHg with pH > 7.20.

Monitoring – in order to be able to always offer the minimum parameter settings during mechanical ventilation and attempt to achieve early weaning from the respirator, it is necessary to monitor ventilation constantly with pulse oximetry and arterial blood gases. Ideal oxygen saturation at the pulse oximeter should be around 90-94%. Therefore, if the infant is receiving supplementary oxygen and presents saturation above 95%, the oxygen supply should be rapidly reduced. Currently accepted levels for arterial blood gas analysis results are: pH = 7.25-7.35; PaO_2 = 50-70 mmHg; $PaCO_2$ = 45-65 mmHg.

High-frequency ventilation

This ventilation modality uses tiny tidal volumes, with respiratory frequencies of 300 to 900 breaths per minute or more, maintaining average airway pressure constant. High-frequency ventilation exposes the alveoli to less pressure variation and this reduces the risk of alveoli distension or collapse. The two primary advantages over conventional ventilation are improved oxygenation and more effective $PaCO_2$ reduction.

The introduction of high-frequency ventilation (high-frequency oscillation - HFO, high-frequency jet ventilation - HFJV and high-frequency flow-interrupted ventilation - HFFIV) was initially received with enthusiasm by neonatologists since it appeared less aggressive and used very small tidal volumes with elevated respiratory frequencies, reducing alveolar distension or collapse and thus reducing the risk of lung injuries. Over the last two decades, however, several different clinical studies have been performed and the results remain controversial.[57-65] Two systematic reviews by the Cochrane Database did not find evidence of great advantages for the use of high-frequency ventilation. Some of the studies involved showed a discrete reduction in the incidence of BPD, while in others there was a significant increase in intraventricular hemorrhage and air leak syndrome.[64,65] Comparing HFO with conventional mechanical ventilation for premature newborn babies, the authors concluded that HFO did not lead to reductions in BPD or mortality, compared to conventional mechanical ventilation, when used as initial treatment for RDS in extremely premature infants.[64]

High-frequency ventilation is nowadays more often used as a rescue therapy in severe respiratory failure refractory to conventional mechanical ventilation or in newborn babies with significant CO_2 retention who also have not improved with conventional mechanical ventilation.

Postnatal Corticosteroids

Corticosteroids have been used during the postnatal period to reduce the pulmonary inflammatory process, but in 2002, the American Pediatric Society and the Canadian Paediatric Society recommended the suspension of dexamethasone use for premature infants after birth due to significant side effects, such as delayed neurological development.[66] Both studies suggested that larger studies were needed with other types of systemic and inhaled corticosteroids before their clinical use could be recommended. Watterberg et al., in a pilot study, observed that premature infants with low concentrations of cortisol developed more exacerbated responses to inflammatory stimuli, increasing the incidence of BPD. Premature infants who received "physiological replacement" with low dose hydrocortisone (1 mg/kg/day divided every 12 hours for 12 days) progressed with reduced incidence of BPD.[67] However, a more recent, multicenter, randomized and controlled study, with a larger population of newborn babies, had to be interrupted because of an observed increase in the incidence of spontaneous intestinal perforation in the group that had received hydrocortisone.[68] Further research is therefore necessary to confirm the possible beneficial effect of hydrocortisone and to assess the side effects. Several studies have attempted to demonstrate the efficacy of inhaled corticosteroids; however, a systematic review of randomized studies did not demonstrate that inhaled corticosteroid reduces the incidence of chronic lung disease.[69]

Because there is no alternative treatment, corticosteroid is still being used at many neonatal intensive care units as a last resort for newborn babies with severe cases of BPD who are dependent on O_2, after consideration of the risks and benefits of the strategy and ruling out other symptoms that cause O_2 dependency, such as patent ductus arteriosus and sepsis. At the most recent Neonatology Symposium held in Miami in November 2004, the use of corticosteroids in low doses for short periods of time (0.2 mg/kg/day 12/12 hours for 3 days) was recommended for these severe cases, but it's use prophylactically and/or in the first week of life was discouraged.

Antioxidants

Nowadays, premature newborn babies are observed to develop BPD even when not exposed to high oxygen concentrations. It is known that premature infants who progress with BPD exhibit both qualitative and quantitative differences in the oxidization of lipids and proteins, when compared with those who do not develop BPD, suggesting that an antioxidant deficiency may increase the risk of BPD.[70,71] Despite these data, there is insufficient evidence of the efficacy of antioxidants for reducing BPD, probably because it is still necessary to better identify the specific oxidation reactions that occur with greatest frequency

among premature infants and the mechanisms of these reactions in order to be in a position to define the administration of a specific antioxidant. It is, however, known that vitamin A has antioxidant effects and studies show a reduction in the incidence of BPD when this vitamin is replaced. Extremely premature infants often exhibit low plasma concentrations of vitamin A[72] and this low concentration is related with increased incidence of BPD.[73] A multicenter study published in 1999 by the NIH demonstrated that intramuscular vitamin A supplementation at a dosage of 5,000 UI, three times a week for 4 weeks, reduced the risk of BPD and increased premature infant survival.[74] More recently, Namasivayam et al. tested different dosages of vitamin A on extremely premature infants and concluded that the dosage proposed by the NIH study remains the best dose for reducing the incidence of BPD without side effects.[75] It is therefore important to recommend vitamin replacement for premature newborn babies and for expectant mothers presenting a deficiency of the vitamin, particularly in deprived areas of developing countries.

Coadjuvant treatments

Supplying nutrition that is rich in calories and proteins as early as possible is necessary to avoid increased catabolism and to reduce oxidant activity. Encouraging maternal milk use in ICUs is of fundamental importance. Recently, in a study by the NIH neonatal network, Duara et al. demonstrated that the incidence of BPD was significantly lower among premature infants fed on their mothers' milk when compared with those that were given formula (OR 0.64; 95% CI% 0.44-0.93; $p < 0.03$).[76] This result is probably due to the immunological qualities and the high concentration of antioxidants in breastmilk.

Reduced fluid intake, early closing of ductus arteriosus and sepsis prevention are other important factors for reducing the incidence of BPD.

Future therapies

To date no single specific therapy exists that significantly reduces the incidence of BPD in isolation. Genetic studies on the theme have showed promising advances, such as the discovery of growth factors that are involved in fetal and neonatal pulmonary and vascular development, of which the following are of special interest: connective tissue growth factor (CTGF), vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-beta), the angiopoietins and the endothelins, among others. The Research Laboratory at the University of Miami Neonatology Division is working on this type of research and recently observed a significant increase in CTGF in the lungs of newborn rats ventilated with large tidal volume, in comparison with those ventilated with normal tidal volume and those that were not ventilated.[77] Along the same lines, it is possible that the discovery of the genes that regulate the inflammatory process and oxygen-generated injuries can generate therapies that will offer adequate alveolar and vascular development for the lungs of extremely premature infants, thus reducing the incidence of BPD.

Furthermore, a number of different recent experimental research projects are attempting to discover a new anti-inflammatory agent that does not have the deleterious effects of corticosteroids. Ter Horst et al. showed that pentoxifylline, a methylxanthine with modulatory effects, reduces fibrin deposits and increases the survival of newborn rats exposed to hyperoxia.[78] Experimental research at our laboratory has shown that pentoxifylline attenuates the increase in inflammatory mediators and also pulmonary edema, after ventilation of rats with large tidal volumes.[79] Similar effects also appear to take place when ibuprofen is used.[80] Multicenter studies are needed to assess the efficacy and collateral effects of these new anti-inflammatories on extremely premature infants.

Another factor of fundamental importance to reducing the incidence of BPD is reducing the occurrence of premature birth. In this context, the NIH and the March of Dimes Birth Defects Foundation are encouraging studies to determine the genetic factors that trigger premature delivery in an attempt to reduce its incidence.

Conclusions

The prevention of lung injury in extremely premature infants requires that the multiple variables contributing to its development be minimized while factors that facilitate the normal development of the lungs are maximized.

The best means of preventing lung damage is to avoid premature delivery. When premature birth cannot be avoided, antenatal corticosteroids should be used to accelerate alveolar and capillary maturation in these infants' lungs. It is important to monitor expectant mothers during the prenatal period for diagnosis and treatment of possible chorioamnionitis and also to treat mothers with vitamin A deficiencies.

Immediately after birth, rapid and correct procedures should be performed to offer these premature infants a safe transition from fetal to neonatal life. The conduct followed in the delivery room itself can have consequences for the rest of these newborn babies' lives. The choice between prophylactic or therapeutic surfactant is still debatable, but when the choice is made to use therapeutic surfactant this must mean administering surfactant as soon as the newborn presents the first signs of respiratory distress, which can take place after a few minutes of life and so the surfactant must be available from the moment of birth.

Adopting prophylactic postnatal surfactant and CPAP or gentle mechanical ventilation will depend on the experience of each center since work published to date does not permit a certain definition of which practice is best. What is important is to employ these techniques correctly, with frequent monitoring and arterial blood gases in order to avoid hypo- or hyper-ventilation. In the case of CPAP as first choice, scientific research appears to indicate that this treatment exhibits more positive results

when used after prophylactic surfactant. In the case of mechanical ventilation, synchronized ventilation should be preferred as permitting lower respirator parameter settings. With respect of gentle ventilation is it of fundamental importance to use small tidal volumes and to set PIP and PEEP adequately for each different pathology, in addition to using shorter inspiratory times to avoid volutrauma. Furthermore, monitoring O_2 levels in order to offer adequate support and acceptance of higher $PaCO_2$ levels are also important strategies for more gentle ventilation.

Studies using antioxidants and new anti-inflammatories are still needed. It is important to emphasize that, through greater knowledge of the genetic factors that determine alveolar and vascular development, it will be possible to obtain new genetic therapies for reducing the incidence of BPD in extremely premature infants.

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