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Review

Prevention and treatment of chronic lung disease

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Abstract

The increased survival among very low birth weight (VLBW) contributes to the overall increase in the incidence of chronic lung disease (CLD), also known as bronchopulmonary dysplasia (BPD), that remains a major complication of prematurity.

The long-term health consequences of BPD include early and long term respiratory disease, susceptibility to respiratory infections, pulmonary hypertension, repeated hospitalizations, neurodevelopmental impairment and increased mortality.

BPD pathogenesis is multifactorial and includes exposure to mechanical ventilation, oxygen toxicity, infection, and inflammation, but the real causes in single individuals have not been well clarified.

In this review the current and potential future postnatal pharmacological (caffeine, diuretics, postnatal corticosteroids, bronchodilators, pulmonary vasodilators, anti-oxidants) and non-pharmacological strategies (ventilatory support, stem cells) in the prevention and management of BPD will be presented.

Keywords

Preterm infant, chronic lung disease, bronchopulmonary dysplasia, prevention, treatment.

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Introduction

Mortality rates among very low birth weight (VLBW) infants have declined due to advances in perinatal care but the increased survival among these infants contributes to the overall increase in the incidence of chronic lung disease (CLD), also known as bronchopulmonary dysplasia (BPD), that remains a major complication of prematurity [1].

The long-term health consequences of BPD include respiratory disease that can persist into adulthood and increased susceptibility to respiratory infections, pulmonary hypertension, repeated hospitalizations, neurodevelopmental impairment and increased mortality [2].

BPD pathogenesis is multifactorial and includes exposure to mechanical ventilation, oxygen toxicity, infection, and inflammation [3]. Multiple pharmacological and non-pharmacological approaches have been proposed for the prevention or treatment of preterm lung injury and BPD [4].

Most current therapeutic measures such as antenatal steroids, surfactant, protective ventilation strategies, targeted oxygen saturation goals, optimization of nutrition have helped to modestly improve BPD though they continue to be supportive [5].

In this review the current and potential future postnatal pharmacological and non-pharmacological strategies in the prevention and management of BPD will be presented.

Pharmacological strategies

Caffeine

Caffeine is a methylxantine used for treatment of apnea of prematurity.

The CAP trial has provided unequivocal evidence for the beneficial effects of caffeine on BPD [6]. In this trial preterm infants with birth weight 500-1,250 g, were randomized to caffeine or placebo within the first 10 days of life. In the caffeine group compared to the placebo group, a significant reduction in BPD at 36 weeks PMA and a reduction in days of mechanical ventilation, were shown. In the long-term follow-up, a reduced incidence of cerebral palsy and neurodevelopmental disability in caffeine-treated group was observed [7].

Although the potential mechanism of the effect of caffeine on decreased incidence of BPD remains unknown, caffeine treatment for prevention of BPD is currently standard of care in most neonatal intensive care units (NICUs).

Diuretics

Diuretics are used in the management of BPD, complicated by interstitial alveolar edema. Excessive fluid administration, capillary leak from inflammation related to infection or lung injury, volume overload due to a patent ductus arteriosus, are all factors contributing to pulmonary edema [8]. Furosemide, the most widely administered loop diuretic in newborns, can improve lung mechanics, increases local prostaglandin leading to pulmonary vasodilation, enhances lung fluid absorption, inhibits bronchial smooth muscle contraction, and decreases inflammatory mediator release. These potential benefits must be balanced against important systemic side effects including electrolyte disturbances, ototoxicity, and renal calcium excretion. Although they are used to treat the symptoms of BPD, there is little evidence of their effectiveness in improving long-term outcomes. A systematic review found that although furosemide improves pulmonary compliance, minute ventilation, and oxygen requirement in infants aged > 3 weeks with BPD, there was no beneficial effect in duration of oxygen requirement or mechanical ventilation [9].

Diuretics acting primarily at the distal tubules, including thiazides and spironolactone, are less potent than loop diuretics but potentially cause fewer electrolyte abnormalities. A systematic review showed that thiazide and spironolactone improved lung compliance and decreased intermittent furosemide; there is little evidence that distal diuretic administration reduces duration of ventilation or length of stay [10].

Despite a lack of evidence to support long-term diuretic use, such use is a routine occurrence in NICUs [11].

Postnatal corticosteroids

Given that inflammation plays a key role in the pathogenesis of BPD, corticosteroid use makes physiologic sense mainly due to their anti-inflammatory properties.

Both systemic and inhaled corticosteroids have been studied extensively in preterm neonates for prevention and treatment of BPD. These clinical trials can be classified as early (≤ 7 days) and late (> 7 days) depending on the timing of administration after birth.

The Cochrane meta-analysis review of twenty-eight clinical trials of early systemic steroids revealed that they facilitated extubation and decreased the incidence of BPD. These benefits do not outweigh the known or potential adverse effects of this treatment (gastrointestinal perforation and cerebral palsy), and it cannot be recommended for routine clinical practice [12].

Another Cochrane meta-analysis reviewed the use of steroids at > 7 days in nineteen RCTs. The benefits of late dexamethasone, including reduction of BPD, may not outweigh actual or potential adverse effects [13]. Both the early and late steroid trials mainly used dexamethasone at high doses (> 0.5-1 mg/kg/day).

Given the available evidence, the early use of dexamethasone in the first week of life is not indicated and it appears prudent to reserve the use of late dexamethasone to infants in whom weaning from high ventilator settings and oxygen support is unsuccessful or respiratory status is rapidly deteriorating [14]. Due to the observed side effects of dexamethasone, hydrocortisone effect has been studied for the prevention of BPD. Although no study showed a clear benefit with hydrocortisone administration, a trend towards decreased mortality and increased survival without BPD was observed in a large clinical trial on preterm infants exposed prenatally to chorioamnionitis [15]. A meta-analysis of the available randomized trials (first week of life) showed little evidence for a direct effect of hydrocortisone on the rates of BPD or mortality. Hydrocortisone in the doses used in the these trials has few beneficial and harmful effects (an increase in gastrointestinal perforation) and cannot be recommended for prevention of BPD [16].

Bronchodilators

Bronchodilators may be indicated in BPD due to increased airway resistance, smooth muscle hypertrophy and hyperreactivity. The two most widely used bronchodilators are salbutamol and ipratoprium.

Short-term studies demonstrated increased respiratory compliance and reduced resistance after bronchodilator treatment in infants with established and evolving BPD [17]. Although these medications target important components of the disease process, studies have shown that responses are variable and often transient. In conclusion, based on current evidence, routine use of bronchodilators for prevention of BPD cannot be recommended.

Pulmonary vasodilators

Pulmonary hypertension is increasingly recognized as a complication of premature birth and BPD. BPD-associated pulmonary hypertension is estimated to occur in 30-45% of infants with moderate to severe BPD and can contribute to the severity and persistence of BPD symptoms and impose additional morbidity and mortality [18]. Animal studies have shown that inhaled nitric oxide (iNO) reduces lung inflammation, improves surfactant function and promotes lung and alveolar growth, suggesting that iNO may be beneficial to prevent or treat BPD [19].

The role of nitric oxide (NO) in preterm infants regarding survival and rate of BPD is controversial. Early use of low-dose iNO in very premature infants did not improve survival without BPD or brain injury, and is thus unsuccessful [20]. Early rescue treatment (< 3 days) with iNO, based on oxygenation criteria, did not seem to affect mortality or BPD rates. Later treatment (> 3 days) based on the risk of BPD showed no effect on the combined outcome of death or BPD. Early routine use for intubated, mildly sick preterm infants showed only a small reduction in the incidence of the combined outcome of death or BPD [21].

In a systematic review a modest reduction in composite outcome of death or BPD was found but there was no reduction in rates of death alone or BPD in infants treated with iNO compared to controls. According to the NIH Consensus Statement, the current available evidence does not support the use of iNO, in care of premature infants, to reduce the occurrence or severity of BPD [22].

Sildenafil is a selective cyclic guanosine monophosphate (cGMP) specific phosphodiesterase inhibitor that results in increased cGMP levels and ultimately increased pulmonary vasodilation. Sildenafil is gaining attention as a potentially useful therapy in infants with oxygenation impairment due to severe BPD or pulmonary hypertension (PH). Animal studies have shown that sildenafil improves alveolar growth and reduces pulmonary hypertension, but there are no available clinical data of this therapy on newborns [23]. Sildenafil citrate should be used cautiously in infants with BPD-associated PH as a

rescue therapy, even with the possibility of longer-term benefits of sildenafil citrate on lung growth [24].

Anti-oxidants

Free radicals are involved in the pathogenesis of BPD and preterm infants have very high susceptibility to oxidative stress because of their deficiency in endogenous antioxidant systems.

Vitamin A is a retinoid essential for normal lung growth and important in regulation of lung epithelial cells repair. Preterm infants are relatively deficient in vitamin A and this has been shown to be associated with BPD. A Cochrane meta-analysis reviewed eight studies on the efficacy of intramuscular vitamin A supplementation in prevention of BPD in ELBW infants, showing a decrease in BPD rate in treated population [25]. The current evidence supports the use of high dose intramuscular vitamin A supplementation for the prevention of BPD in preterm infants < 1,000 g, although no long-term benefits in pulmonary or neuro-developmental outcome were found [26].

Vitamin E and vitamin C both play a role as scavengers of reactive oxygen species producted during high oxygen exposure and they prevent lipid peroxidation, potentially limiting the processes that lead to BPD. RCTs have showed no evidence that vitamin E supplementation alone or associated to vitamin C have a protective effect against BPD [27]. Preliminary animal and human studies have demonstrated a protective effect of anti-oxidants like superoxide dismutase (SOD) in hyperoxia-induced acute and chronic lung injury [28]. A RCT evaluated pulmonary outcome at 1 year in premature infants treated with recumbinant SOD. No difference was found in BPD at 28 days of life or 36 weeks PMA in treatment group compared to the placebo [29]. Gluthatione is an endogenous scavenger of free radicals, relatively deficient in premature infants with decreasing gestational age. N-Acetyl Cysteine (NAC) is a gluthatione precursor, potentially capable to ameliorate cellular injury from free radicals. No significant results in terms of difference of incidence or severity of BPD were found in preterm infants treated with NAC [30].

Non-pharmacological strategies

Ventilatory support

Mechanical ventilation is an important risk factor in the pathogenesis of BPD and lung protective ventilation remains an important intervention in the prevention of BPD. Optimization of neonatal respiratory support starts during the resuscitation period and a protective strategy is achieved through the definition of adequate oxygenation ranges and tailored ventilation [31].

In mechanical ventilation, the volume targeted ventilation had reduced death or BPD compared with pressure-limited ventilation and is associated with a reduced risk of pneumothorax, hypocarbia, duration of ventilation and severe intraventricular hemorrhage [32].

Since BPD currently has no specific preventive or effective therapy, considerable interest has focused on the use of non-invasive ventilation (NIV) as a means to potentially decrease the incidence of BPD [33].

Over the last decade, nasal continuous positive airway pressure (NCPAP) has been increasingly used to manage preterm infants in the delivery room and in the neonatal intensive care unit as primary treatment of RDS or post-extubation [34]. Anecdotal evidence and small RCTs have suggested that early NCPAP use could lead to a decreased incidence of BPD [35, 36]. However, this has not been confirmed by larger RCTs that compared extremely preterm neonates randomized to NCPAP or intubation at birth [36, 37].

Nasal intermittent positive pressure ventilation (NIPPV) is another approach of NIV in which the nasal intermittent positive pressure ventilation is given via nasal prongs and creates intermittently elevated pharyngeal pressures [38]. Studies on NIPPV demonstrated a statistically significant benefit for infants extubated to NIPPV compared to NCPAP to prevent extubation failure and to reduce the frequency of apneas [39]. These benefits were associated with a trend towards lower rates of chronic lung disease, but did not reach statistical significance; that was partly related to small sample size of the studies [40].

In a largest retrospective analysis comparing synchronized NIPPV to NCPAP use in preterm neonates, after controlling for confounding variables, use of SNIPPV in the birth-weight category of 500-750 g was associated with decreased BPD and BPD/death [41].

Recently high flow nasal cannula (HFNC) is emerging as an efficient, better tolerated form of NIV, allowing better access to the baby and improving nursing. Humidified and optimally warmed respiratory gases are given by nasal cannula at flow rates between 2 and 8 L/min. Although a growing

evidence of the feasibility of HFNC as an alternative mode of NIV, its clinical efficacy and safety are still insufficiently investigated and therefore insufficient data on rate of BPD are available [42].

It was demonstrated that the mode of respiratory support in the first week of life was correlated with the outcome of BPD/death. In a multivariate analysis, when compared with endotracheal intubation, NIPPV and NCPAP groups were less likely to have BPD/death [43].

Stem cells

Recent advances in understanding of stem cells and their potential to repair damaged organs offer the possibility of cell-based treatments for neonatal lung injury.

Although there are currently no published clinical trials on the use of stem cells in treating or preventing BPD, significant progress in our understanding of stem cell therapy for BPD has been achieved. Recent animal and human studies suggest that damage or depletion of stem cells in the developing lung likely contributes to the pathogenesis of BPD [44]. In experimental models, mesenchimal stem cells (MSCs) are the most extensively examined cell type. Numerous aspects of neonatal lung injury have been ameliorated by the administration of either bone marrow-derived or umbelical cord blood-derived MSCs. The MSCs exerted their therapeutic effects by mitigating lung inflammation, preventing lung vascular damage and alveolar growth impairment, inhibiting lung fibrosis, and improving exercise tolerance [45].

Some studies support the notion that the potential mechanisms through which MSCs exert their actions are paracrine mediated, and that the therapeutic benefit of MSC-conditioning media may surpass that of MSCs, alleviating some concerns, such as the possibility of tumor formation [46].

No definitive human studies or results have yet to show benefits, but preclinical studies are ongoing and suggest great promise for future potential therapies for BPD [44].

Declaration of interest

The Authors declare that there is no conflict of interest.

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