PREGLED LITERATURE – REVIEW ARTICLE

Bronchopulmonary dysplasia: treatment and prevention

Bronhopulmonalna displazija: tretman i prevencija

Cerovic Sofija[1], Zivkovic Zorica[1,2], Vekovic Vesna[1], Vekovic Borko[3]

[1]Children's Hospital for Lung Diseases and Tuberculosis, Medical Center "Dr Dragiša Mišović", Belgrade, Serbia

[2] Faculty of Pharmacy Novi Sad, Business Academy Novi Sad, Serbia

[3]Institute of Neonatology, Belgrade, Serbia

Summary Since 1967, when it was first defined and described the nature and definition of bronchopulmonary dysplasia (BPD) has evolved. Based on clinical and radiographic evidence of pulmonary disease in moderately to late premature infants with a history of respiratory distress syndrome, BPD was familiarly defined as a chronic form of lung disease in neonates treated with oxygen and positive pressure ventilation for a primary lung disorder, the nature of BPD has evolved into a "new" form of BPD typically seen in neonates surviving at the threshold of viability and characterized primarily by arrest of alveolar and vascular development. Infants develop BPD in about 1.5% of all newborn births. The incidence of BPD appears to be growing in conjunction with the increased survival of very-low-birth-weight infants who are treated for and recover from respiratory distress syndrome (RDS). This review has been an up-date of literature data, including animal studies, human pilot studies, randomized controlled trials (RCTs), meta-analyses and systematic reviews published on the PubMed data base

Key words: bronchopulmonary dysplasia, prematurity, review

Sažetak Bronhopulmonalna displazija (BPD) opisana je prvi put 1967. godine. Tadašnja definicija BPD zasnivala se na kliničkim i radiografskim znacima plućne bolesti kod prevremeno rodjene dece, koja su bila na mehaničkoj ventilaciji sa pozitivnim pritiskom i dugotrajno na terapiji kiseonikom. U današnje vreme, BPD se karakteriše zastojem u razvoju alveolarnih i vaskularnih struktura kod prevremeno rodjene dece. BPD se javlja u 1,5% sve novorodjene dece. Incidecna BPD se povećava u skladu sa sve većim preživljavanjem prevremeno rodjene dece, a posebno dece sa vrlo malom porodjajnom težinom, koja su lečena i oporavila se od respiratornog distres sindroma. Ovaj rad je pregled savremene literature, uključujući studije na životinjama, u humanoj populaciji, randomizovane kontrolisane studije, meta analize i sistematski pregled PubMed podataka.

Ključne reči: bronhpulmonalna displazija, prevremeno rodjenje, pregled literature

Introduction

Since 1967, when it was first defined and described by Northway et al., the nature and definition of bronchopulmonary dysplasia (BPD) has evolved. Based on clinical and radiographic evidence of pulmonary disease in moderately to late premature infants with a history of respiratory distress syndrome, BPD wasfamiliarly defined as a chronic form of lung disease in neonates treated with oxygen and positive pressure ventilation for a primary lung disorder (1), the nature of BPD has evolved into a "new" form of BPD typically seen in neonates surviving at the threshold of viability and characterized primarily by arrest of alveolar and vascular development (2-5).

In 2008 the National Institute of Child Health and Human Development (NIH) defined and classified BPD capturing criteria from previous definitions and incorporating a stratification system based on clinical severity by gestational age and supplemental oxygen requirement.

Infants <32 weeks postmenstrual age presenting with clinical manifestations of the disease, requiring supplemental oxygen at 28 days of life, and who were weaned to room air by 36 weeks or at discharge were considered to have mild BPD. Infants requiring <30% continuous oxygen at 36 weeks postmenstrual age or at discharge were considered to have moderate disease. Infants remaining on 30% oxygen and on continuous positive airway pressure (CPAP) were considered to have a severe form of the disease. For infants 32 weeks gestation, the identical oxygen requirement was implemented at day of life 56 (6).

Infants develop BPD in about 1.5% of all newborn births. The incidence of BPD appears to be growing in conjunction with the increased survival of very-low-birth-weight infants who are treated for and recover from respiratory distress syndrome (RDS) (7, 8).

Methods

Approximately 80 articles, including animal studies, human pilot studies, randomized controlled trials (RCTs), meta-analyses and systematic reviews published on the PubMed data base were evaluated for inclusion in this article.

DIURETICS

Furosemide (Lasix) is the treatment of choice for fluid overload in infants with BPD. Furosemide acts on the ascending loop of Henle and blocks chloride transport. Additionally, furosemide reduces interstitial edema and pulmonary vascular resistance and increases plasma oncotic pressure and lymphatic flow. It is the treatment of choice for fluid overload in BPD. Daily or alternate day furosemide therapy may ease weaning from positive pressure ventilation (PPV), oxygenation or both. Adverse effects of long-term therapy are recurrent and include hyponatremia, hypokalemia, contraction alkalosis, hypocalcemia, hypercalciuria, renal stones, nephrocalcinosis and ototoxicity. However, long-term benefits have not been established in infants with BPD (9, 10,11,12).

Thiazide diuretics plus aldosterone inhibitor have also been used in infants with BPD. In several trials of infants with BPD, thiazide diuretics combined with spironolactone increased urine output with or without upgrading in pulmonary mechanics. Hoffman et al reported that spironolactone did not reduce the need for supplemental electrolytes in preterm infants with bronchopulmonary dysplasia(13).

Overall, diuretics offer short-term enhancements in pulmonary mechanics but are related to a number of side effects that may limit longer term use (e.g., ototoxicity, electrolyte disturbances, azotemia, etc.). In addition, there are partial data demonstrating significant benefits of these agents when more expressive outcome measures are analyzed such as reduction in the duration of mechanical ventilation and hospitalization or improved long- term clinical outcomes (less asthma, pulmonary infections, etc.).

BRONCHODILATORS

Albuterol may improve lung compliance by decreasing airway resistance by relaxing smooth muscle cell. While a Cochrane review examining the role of albuterol was unable to find sufficient evidence of efficacy in the prevention of BPD, other studies have shown improvement in pulmonary mechanics following treatment (14,15). In summary, long-term efficacy has not been recognized and tolerance may develop with prolonged use.

Ipratropium bromide is a muscarinic antagonist that is related to atropine; however, it may have bronchodilator effects more potent than those of albuterol. Enhancements in pulmonary mechanics were demonstrated in patients with BPD after they received ipratropium bromide by inhalation. However, clinical trials have not demonstrated changes in the natural progression of BPD or long-term clinical respiratory status (16,17).

METHYLXANTHINES

Caffeine treatment for the prevention of apnea of prematurity and BPD is currently the standard of care in most neonatal intensive care units. (18) Methylxanthines are used to increase respiratory drive, decrease apnea, and improve diaphragmatic contractility. These substances may also decrease pulmonary vascular resistance and increase lung compliance in infants with BPD, probably by directly causing smooth muscle to relax.

Schmidt et al. conducted a large, multicenter RCT investigating the effects of caffeine on apnea of prematurity in a cohort of infants weighing 500–1250 g at birth (19). Less BPD, patent ductus arteriosus (PDA), and cerebral palsy when followed out to 18–21 months corrected gestational age (20) did not translate into longer-term benefits when this same cohort of infants was examined at 5 years of age (21).

VITAMIN A

Vitamin A is important in maintaining cell integrity and promoting tissue repair with deficiencies producing significant changes in the tracheobronchial tree (22).
Multiple studies have demonstrated that very low birth weight infants are deficient in Vitamin A and at a propensity to develop BPD (23, 24).

Seven trials of vitamin A supplementation in preterm neonates to prevent BPD were analyzed for the Cochrane Collaborative Neonatal review. Vitamin A supplementation reduced BPD and death at 36 weeks' postmenstrual age.

CORTICOSTEROIDS

Systemic and inhaled corticosteroids have been studied extensively in preterm infants to prevent and treat BPD.

Dexamethasone is the primary systemic synthetic corticosteroid studied in preterm neonates. This drug stabilizes cell and lysosomal membranes, increases surfactant synthesis, increases serum vitamin A concentration, inhibits prostaglandin and leukotriene, decreases pulmonary edema (PE), breaks down granulocyte aggregates, and improves pulmonary microcirculation. Its adverse effects are hyperglycemia, hypertension, weight loss, GI bleeding or perforation, cerebral palsy, adrenal suppression, and death.

Papile et al. stated that early use of dexamethasone during the first 2 weeks of life did not prevent BPD and may worsen neurologic outcome (25). Infants who received a combination of dexamethasone and indomethacin were at enlarged risk of spontaneous intestinal perforation. Neurodevelopmental follow-up studies of infants treated with prolonged and high-dose dexamethasone suggest that long-term outcome appears to considerably worsen.

Inhaled steroids have been observed as a therapeutic approach to the treatment of BPD in order to promote respiratory benefits while reducing systemic side effects. Studies examining the benefits of inhaled corticosteroids administered early or late have not been able to validate any effect of inhaled corticosteroids on short-term respiratory outcomes or longer-term clinical respiratory status (26, 27).

Additionally, inhaled corticosteroids appear to offer no clinical advantage over systemic steroid therapy (28).

VASODILATORS

Infants with BPD can experience intermittent episodes of hypoxia which can promote secondary pulmonary vasoconstriction and pulmonary hypertension, adding to the complexity of BPD (29, 30). This has caused much interest in the selective pulmonary vasodilator nitric oxide (NO) as alterations in NO signaling, vascular growth, and reactivity appear to play a role in the development of BPD (31, 32).
Multiple randomized controlled trials of iNO in preterm infants have been performed using varying entry criteria and outcomes. The results are mixed.

Ballard et al demonstrated a modest but statistically significant benefit in survival without BPD at 36 weeks PMA. (33) Evidence from Van Meurs etal. Indicate a high errate of mortality and intraventricular hemorrhage (IVH) in infants weighing <1000 g at birth who received inhaled NO (34). Large meta-analyses have been unable to find steady long-term improvement in mortality or the incidence and severity of BPD when using inhaled NO in preterm infants as a prevention or rescue therapy (35, 36).

LATE SURFACTANT

Surfactant replacement was established as an effective and safe therapy for immaturity-related surfactant deficiency by the early 1990s (37). Systematic reviews of randomized, controlled trials confirmed that surfactant administration in preterm infants with established respiratory distress syndrome (RDS) reduces mortality, decreases the incidence of pulmonary air leak (pneumothoraces and pulmonary interstitial emphysema) and lowers the risk of chronic lung disease or death at 28 days of age (38,39,40). Subsequent trials indicated that prophylactic or early administration of surfactant resulted in fewer pneumothoraces, less pulmonary interstitial emphysema, and improved survival without BPD (41,42,43,44). However, recent randomized clinical trials indicate that the benefits of prophylactic surfactant are no longer evident in groups of infants when continuous positive airway pressure (CPAP) is used routinely (45,46,47).

ANTIOXIDANTS

Different antioxidant strategies are under development in order to prevent and treat respiratory diseases of prematurity, particularly with the scope of BPD prevention, since present preventive strategies and medical treatment are certainly suboptimal. Melatonin (MT) has been poorly explored for this indication as far as now, but encouraging results were obtained in preterm newborns and animal models, indicating melatonin induced suppression of oxidative stress (OS) pathways and upregulation of antioxidant enzymes (AOEs). These data suggest that MT may be considered as an appreciated candidate for future researches in this field. Recent evidence also suggests potential protective effects of AOEs supplementation or overexpression against OS induced lung injury. However, only a minority of available data were obtained from clinical settings; therefore larger clinical trials are mandatory in order to clarify therapeutic potentials of such strategies.

Conclusion

BPD is a complex multisystem disease that carries a important physical, social, and economic burden for the survivors and their families. While multiple therapies are used regularly either alone or in combination (potentially increasing drug–drug interactions and associated side effects), there is lack of evidence supporting short and longer-term use of many of these agents. In fact, no single therapy has been shown to have a significant impact on the incidence or severity of BPD. Future research should be aimed at establishing better biomarkers predictive of BPD and associated longer-term chronic respiratory morbidity, developing models to identify high-risk infants earlier, and applying a multimodal approach when studying various pharmacologic interventions.

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Correspondance to:
Sofija Cerović
cerovicsofija@yahoo.com