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Review

News on neonatal respiratory research

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Learned lessons, changing practice and cutting-edge research

Abstract

We aimed to assess some of the most recent advances in the pulmonary neonatal medicine. For this purpose we reported on the role of the sustained lung inflation (SLI) procedure in the delivery room, the development of new exogenous surfactant preparations, the effectiveness of nasal high frequency ventilation (nHFV), and the treatment of patent ductusarteriosus (PDA) with paracetamol. Moreover, we discussed the possible future role of nanomedicine and stem cells in the treatment of BPD.

Keywords

Sustained lung inflation, surfactant, nHFV, paracetamol, infant, BPD.

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Introduction

Although the respiratory support of extremely preterm infants with respiratory distress syndrome (RDS) has improved and new strategies have been developed, the mortality of these patients is still high and the occurrence of bronchopulmonary dysplasia (BPD) has remained substantially

unchanged. In particular BPD occurs in 20-60% of preterm neonates with an inverse relationship with gestational age [1].

Thus, our aim was to assess the recent advances that, in our opinion, could contribute to improve the respiratory outcome of extremely preterm infants. For this purpose we selected the following arguments: the sustained lung inflation (SLI) procedure in the delivery room, the new exogenous surfactant preparations, the nasal high frequency ventilation (nHFV), the treatment of patent ductus arteriosus (PDA) with paracetamol, and the possible future role of nanotechnology and stem cells in the treatment of BPD.

The sustained lung inflation

One aspect of respiratory care in preterm infants which has not yet been thoroughly investigated is respiratory assistance in the delivery room immediately after birth. In fact, lung protection against ventilator-induced lung injury (VILI) should start in the delivery room where, from the first breaths, the preterm infant can be helped to clear the lung fluid; to recruit alveolar spaces facilitating the formation of the functional residual capacity (FRC); to protect the lung by avoiding large tidal volume; to avoid the continuous "opening and closing" of the alveoli by delivering positive end-expiratory pressure (PEEP); and to verify the need for surfactant replacement [2, 3].

Recently, some studies have investigated the effectiveness of the early sustained lung inflation (SLI) procedure in preterm infants for prevention of MV. This strategy would permit lung recruitment immediately after birth through delivery of brief peak pressure to the infant airways via a nasopharyngeal tube or mask allowing preterm infants to achieve FRC. To avoid lung collapse at the end of the expiration, the effect of PEEP is crucial. SLI and PEEP seem to have an additive effect on adequate FRC formation by permitting optimal gas exchange, improving lung mechanics and reducing the need for respiratory support.

This technique has been proven to be more effective than intermittent mandatory ventilation (IMV) in improving FRC in the asphyxiated term newborn [4, 5]. Lindner et al. treated preterm infants by using SLI in the delivery room without significant decrease in the MV rate or adverse effects in comparison with treatment with nasal-IMV (N-IMV) noted [6]. On the other hand, te Pas et al. treated preterm infants with repeatable SLI maneuvers and found a decrease in the need for MV at 72 hours of life and BPD in comparison with treatment in the delivery room with a self-inflating bag [7]. These results are in agreement with the findings of a recent paper from the same group which demonstrates the synergistic effect of SLI and following subsequent treatment with PEEP [delivered by nasal continuous airway pressure (nCPAP)] in achieving and maintaining a FRC improvement in animal model [8]. Moreover, Lista et al. recently reported that SLI followed by the delivery of nCPAP is effective in reducing the need of MV and the occurrence of bronchopulmonary dysplasia in survivors compared to nCPAP alone [9].

Therefore, we recently performed a randomized controlled trial [10] in preterm infants with gestational age 25^{+0}-28^{+6} weeks of gestation which compared the application of SLI followed by nCPAP with nCPAP alone in the delivery room to evaluate its effectiveness in decreasing the need of MV and improving respiratory outcome. The results of this study are promising and are currently under conclusive analysis.

New surfactant preparations

Many studies investigated the effectiveness of surfactant in preterm infants with RDS and it has been demonstrated that surfactant decreases pneumothorax and mortality rate [11-13]. Although many questions were answered, other issues are not yet cleared and may deserve considerations such as the role of new synthetic surfactants preparation or the improvement of their effectiveness by combining them with anti-inflammatory and antioxidant drug.

Lucinactant (Discovery Laboratories, Doylestown, PA, USA) is a recently developed synthetic surfactant preparation containing an aqueous dispersion of phopholipids and peptide fragments that mimic domains of surfactant protein B (SP-B) which is called sinapultide (KL4 peptide) [14]. No statistically different clinical differences in death and chronic lung disease were noted between lucinactant and a non-protein-containing synthetic surfactant (colfoscerilpalmitate; GlaxoSmithKline, Brentford, United Kingdom) [15], or between lucinactant and animal derived surfactants (beractant: Abbott Laboratories, Abbott Park, IL, USA; poractant: Chiesi Farmaceutici S.p.A., Parma, Italy) in the prevention of neonatal RDS and RDS-related death [16]. These results are promising, but lucinactant is not commercially available in Europe.

Sato and Ikegami compared the effectiveness of a new synthetic surfactant (CHF5633; Chiesi Farmaceutici S.p.A.) containing dipalmitoyl-phosphatidylcholine, phosphatidylglycerol, SP-B analog, and SP-C analog to that of beractactant in preterm lambs [17]. They found that CHF5633 was effective in treating preterm lamb with surfactant deficiency; moreover, dynamic compliance, tidal volume, and lung volume were higher in CHF5633-treated animals than in beractant-treated animals [17].

The role of inflammatory and oxidative injuries of lung tissues in the pathogenesis of BPD has been well documented [18, 19]. Therefore, we performed a study in preterm lambs, where the lung tissue inflammation and oxidative stress following the treatment with natural surfactant plus beclomethasone or sole natural surfactant were compared. We found that poractant combined with beclomethasone is effective in reducing the inflammation [20] and oxidative lung stress, and improving the respiratory function in this model of RDS [21]. Subsequently, we assessed the effects of poractant combined with superoxide dismutase (SOD) and catalase (CAT) on pulmonary oxidative stress in the same animal model. We demonstrated that this combination was effective in decreasing total hydroperoxide (TH), advanced oxidation protein products (AOPP), and non protein bound iron (NPBI) in bronchial aspirate samples of animals in comparison with sole natural surfactant [22].

The nasal high frequency ventilation

The nHFV is a strategy that could combines the advantages of non-invasive respiratory support and high frequency ventilation, which have been reported to limit the development of ventilator-induced lung injury. Some clinical studies demonstrated that nHFV is effective in decreasing pCO_2 in preterm [23, 24] and term [24, 25] infants with respiratory failure. Mukerji et al. reported that the CO_2 clearance of nHFV is 3-fold higher than that of non invasive positive pressure ventilation (NIPPV) in a neonatal lung model, being the clearance inversely proportional to frequency and maximal at 6 and 8 Hz [26]. Moreover, Rehan et al. demonstrated in preterm lambs that nHFV promotes the synthesis of key homeostatic alveolar epithelial mesenchymal markers which are crucial during the period of alveolarization and whose synthesis is inhibited by intermittent mandatory ventilation (IMV): these findings could be the basis of a possible reduction of the risk of BPD development following nHFV compared to MV [27].

Treatment of PDA with paracetamol

PDA is a frequent complication in preterm infants suffering from RDS, and 60% to 70% of preterm infants of < 28 weeks' gestation receive medical or surgical therapy for a PDA [28]. Neonates with a left-to-right shunt through the ductus complicating their RDS have higher respiratory failure, lower survival rate, and increased risk of intracranial haemorrhage (ICH), bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC) [29]. Therefore, closure of PDA is indicated before a significant left-to-right shunting occurs. PDA can be treated effectively with intravenous indomethacin and ibuprofen, leading to permanent ductal closure in 60% to 80% of infants [30-32]. Preterm infants treated with ibuprofen experience lower serum creatinine values, higher urine output, and less undesirable decreased organ blood flow and vasoconstrictive adverse effects than indomethacin-treated patients [31]. However, also ibuprofen can cause adverse effects.

Therefore, the recent publication of case-series reporting on the effectiveness of paracetamol in closing PDA is very interesting. Paracetamol inhibits prostanoid synthesis by scanging peroxynitrite, which acts as an endogenously formed cellular activator of prostaglandin endoperoxide H2 synthase (PGHS) [33]. It has been found to be effective at 60 mg/kg/day, in four divided doses, for a period of three days both administered orally [34] or intravenously [35]. These reports support the urgent need of randomized controlled trials to establish both the effectiveness and safety of paracetamol for the treatment of PDA in preterm infants.

Future researches

Nanomedicine is the medical application of nanotechnology. Generally, nanomedicine uses nanoparticles which are sized between 1 and 100 nanometers. One of the most important potential clinical application of nanotechnology is the possibility of delivering drugs to specific cells using nanoparticles as vehicle. The overall drug consumption and side-effects may be lowered significantly by depositing the active agent in specific areas and in no higher dose than needed. The potential benefits of nanoparticle in Neonatology has been already demonstrated by some promising

studies in animal models of cerebral palsy [36] and perivetricular leukomalacia (PVL) [36]. However, it has been demonstrated that nanoparticles are effective also in drug delivery to the lung [37] and, therefore, they could have a role in improving the pharmacologic treatment of a chronic lung disease, such as BPD.

Another recent advance has been represented by studies which demonstrate the potential effectiveness of stem cells in the treatment of BPD. Although, many different types of stem cells have been used in experimental model (mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), amnion epithelial cells (AECs), and perivascular cells (PCs), MSCs are the most extensively investigated. However, the finding that the use of conditioned media from MSCs is effective in promoting lung repair by protecting alveolar epithelial and microvasculature endothelial cells from oxidative stress, and preventing oxygen-induced alveolar growth impairment, is very intriguing. In fact, this suggests that the beneficial effects of MSCs might be due to paracrine mechanisms. On the other hand, the treatment of BPD with conditioned media from MSCs, rather than with MSCs, could be more feasible and enter in the clinical practice earlier than a cellular therapy.

Conclusions

The respiratory support of extremely preterm infants represents a great challenge for neonatologists. Many progresses have been made but further advances are necessary to improve the outcome of these patients. Certainly the sustained lung inflation (SLI) procedure in the delivery room, development of new exogenous surfactant preparations, use of nHFV, and treatment of PDA with paracetamol could represent further useful tools for the neonatal care, although randomized controlled studies investigating their effectiveness and safety are needed before they enter in the routine clinical practice. Similarly, further researches are necessary to elucidate the potential benefits of nanomedicine and stem cells therapy in the treatment of BPD.

Declaration of interest

There is no potential conflict of interest to declare. I confirm that there is not any professional affiliation, financial agreement or other involvement with any company whose product figures prominently in the submitted manuscript.

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