REVIEW ARTICLE

Surfactant therapy in meconium aspiration syndrome (MAS)

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ABSTRACT

Meconium aspiration syndrome (MAS) is an important cause of respiratory distress in neonates, sometimes leading to respiratory failure and even death. It is a common problem seen in the delivery room and newborn units. MAS is found in around 2-9% of births and mortality rate is 3-5%. MAS results from aspiration of meconium during intrauterine gasping or during the first few breaths. There is a significant disturbance of the alveolar surfactant system in MAS as an important element in the pathophysiology of the disease. Therapy for MAS is mainly supportive. But, because of the presence of disturbance in the alveolar surfactant system, administration of exogenous surfactant preparations is recommended. Recently, bronchoalveolar lavage is being recommended.

Key words: Meconium, aspiration, neonates, surfactant, surfactant therapy, bronchoalveolar surfactant therapy.

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Background

Meconium aspiration syndrome (MAS) is a common problem seen in the delivery room and newborn units as an important cause of respiratory distress in neonates, sometimes leading to respiratory failure and even death [1, 2].

Therapy for MAS is mainly supportive, but use of innovative treatments such as high-frequency ventilation or inhaled nitric oxide has increased and seems to be of benefit to patients who are refractory to conventional mechanical ventilation [2, 3]. There is a significant disturbance of the alveolar surfactant system in MAS as an important element in the pathophysiology of the disease [4, 5]. This rationalizes administration of exogenous surfactant preparations in MAS, initially as standard bolus therapy and, more recently as broncheoalveolar lavage [6, 7].

Introduction

According to working definitions of the National Neonatal-Perinatal Database of India 2002-03:

MAS should be diagnosed if any two of the following three criteria [8] are present:

(i) Meconium staining of liquor or staining of nails or umbilical cord or skin, presence of meconium in oropharynx or trachea or both.

(ii) Respiratory distress soon after birth, within one

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hour of birth.

(iii) Radiological evidence of aspiration pneumonia with areas of atelectasis and/or hyperinflation

Cleary and Wiswell [9] have proposed a severity criterion to define MAS:

(a) Mild MAS when it requires less than 40% oxygen for less than 48 hours,

(b) Moderate MAS when it requires more than 40% oxygen for more than 48 hours with no air leak, and

(c) Severe MAS when it requires assisted ventilation for more than 48 hours and is often associated with PPHN.

Epidemiology of MAS

Meconium [Greek word `meconium-arion' meaning poppy juice or opium-like], the first intestinal discharge of newborn, is black-green in color, thick, viscous, sticky, odourless and acidic in nature, containing gastrointestinal secretions, bile, bile acids, mucus, pancreatic juice, blood, swallowed vernix caseosa, lanugo, and cellular debris. At birth term neonate passes about 60-200 gms of meconium [10]. Meconium-stained amniotic fluid is found in 8-20% of births out of which about 2-9% suffers from Meconium Aspiration Syndrome (MAS) [11]; mortality being 3–5%. About one-third of infants with MAS require intubation and mechanical ventilation [12]. Because meconium is rarely found in the amniotic fluid prior to 34 weeks gestation, Meconium aspiration syndrome (MAS) generally occurs in term or post-term infants and may be associated with severe respiratory failure and persistent pulmonary hypertension. The incidence of meconium stained amniotic fluid increases with rise in gestational age beyond maturity. Around 23-52% babies may pass meconium in-utero beyond 42 weeks of gestation [13].

Factors that promote the passage of meconium in utero include placental insufficiency, maternal hypertension, preeclampsia, oligohydramnios, and maternal drug abuse, especially of tobacco and cocaine [14]. Factors associated with the development of MAS among babies with MSAF include thicker consistency of meconium, non-reassuring fetal heart tracing, fetal acidosis, cesarean delivery, infants who needed intubation at birth, and a low Apgar score [12, 15].

Pathophysiology of MAS

MAS results from aspiration of meconium during intrauterine gasping or during the first few breaths. Fetal hypoxic stress can stimulate colonic activity, resulting in the passage of meconium and also stimulates fetal gasping movements that result in meconium aspiration in-utero. Evidences suggest that a chronic in utero insult may be responsible for most cases of severe MAS as opposed to an acute peripartum event [16].

The pathophysiology of MAS is complex. Aspirated meconium can interfere with normal breathing and respiration by several mechanisms. These include:

(a) Acute airway obstruction

Depending on the consistency and amount of meconium aspirated, meconium may lead to either partial or complete airway obstruction leading to hyperinflation or atelectasis of the alveoli. The gas trapped may rupture resulting in air leak syndromes such as pulmonary interstitial emphysema, pneumothorax, and pneumomediatinum.

(b) Surfactant dysfunction and/or inactivation

In vitro studies have shown that meconium interferes with surfactant in several ways: inactivation of its function, direct toxicity on type II pneumocytes, displacement of surfactant from the alveolar surface, and decrease in surfactant protein A and B levels [9, 17].

The exact mechanisms for meconium-induced inactivation of pulmonary surfactant are still not clearly understood but is believed to be related to both the consistency of the meconium and the concentration of the surfactant itself [18]. Meconium can impair pulmonary surfactant by a combined action of cholesterol and bile acid present in meconium [19].

(c) Chemical pneumonitis

Meconium is a good chemoattractant for neutrophils [20]. Within a few hours, neutrophils

and macrophages are found in the alveoli, larger airways, and lung parenchyma. Meconium is also a source of vasoconstrictive and proinflammatory mediators such as interleukins (IL-1, IL 6, and IL 8), tumor necrosis factors. Thus it may induce inflammation either directly or indirectly through the stimulation of oxidative bursts in neutrophils and alveolar macrophages and may injure the lung parenchyma or lead to vascular leakage causing toxic pneumonitis and hemorrhagic pulmonary edema [9].

(d) PPHN with right-to-left extrapulmonary shunting

Meconium induces an acute concentration-dependent pulmonary hypertensive response in about 15–20% of infants with the MAS. PPHN in infants with MAS may be caused by (a) pulmonary vasoconstriction secondary to hypoxia, hypercarbia, and acidosis, (b) hypertrophy of the postacinar capillaries as a result of chronic intrauterine hypoxia, and (c) pulmonary vasoconstriction as a result of pulmonary inflammation [4].

Surfactant

Discovered in the early twentieth century, surfactant is a biologic agent found in the lungs that reduces surface tension to facilitate adequate respiration at the bronchio-alveolar level. It is a chemical compound composed of phospholipids (90%) and proteins (10%). The main lipid component is saturated dipalmitoyl phosphatidylcholine (DPPC). The remaining lipids include free cholesterol and negatively charged phospholipids. Four surfactant-associated proteins (SP) have been identified and designated as SP-A, SP-B, SP- C, and SP-D. They are produced by and secreted from type II alveolar cells and Clara cells of the respiratory epithelium.

Exogenous surfactants are conventionally classified into three families [21]

(A) The mammalian or animal-derived surfactant preparations (so-called ‘‘natural surfactant). These are purified and extracted with organic solvents from either lung minces or lung lavages. Their phospholipid concentration is above 80%, and all contain the low-molecular hydrophobic proteins SP- B and SP-C;

(B) The first generation of synthetic surfactant preparations (‘‘artificial surfactant") These are composed mainly of DPPC and are protein-free; and

(C) The emerging second generation of synthetic surfactant. These contain recombinant surfactant proteins or synthetic peptides whose spatial structure resembles the whole or part of SP-B or SP-C.

A fourth category is human surfactant derived from amniotic fluid obtained during elective caesarean section. Because of the inherent difficulties in collecting this material, it never has been practical on a widespread scale.

The difference between natural and synthetic surfactants appears to be that the synthetic surfactants have a delayed onset of action; 12-18 hours after administration as in comparison to natural surfactants which acts earlier and are more effective [22].

Mechanism of action:

The hydrophilic character of SP-B and SP-C helps in uniform spread of surfactant within the terminal airway. More recently, it has been discovered that the surface tension of conducting airways is about 15 mJ/m^2 (ranging between 2 mJ/m^2 at the alveolar level and 32 mJ/m^2 at that of trachea). Thus surface tension is regulated along the entire length of the respiratory tract and not just at the alveoli.

The function of surfactant is twofold. First and most notably, it reduces surface tension in the alveoli, thereby stabilizing lung volume at low transpulmonary pressures as in accordance with Laplace’s law [$\delta P = 2\gamma/r$, where γ, surface tension; r, alveolar radius and δP, pressure gradient]. In surfactant deficiency or inactivation, larger alveoli expand more to compensate for the collapse of the small alveoli, increasing the risk for pneumothorax. Surfactant replacement equalizes the pressures exerted on the different-sized alveoli and thus reduces the incidence of air leak and increases lung volumes. This, in turn, significantly

increases the functional residual capacity of the lungs.

Exogenous surfactant replacement does not inhibit the endogenous production and secretion of surfactant. The surfactant is absorbed slowly into lung tissues and then catabolized.

Dosage and administration techniques:

Dosages ranging between 50 and 200 mg/kg according to the manufacturers' recommendations with retreatment done up to four times in the first 24 hours (maximum of four doses of Survanta, given every 6 hours; two of Curosurf, given every 12 hours; and three doses of Infasurf, also given every 12 hours). It should be instilled rapidly into the trachea as early as practicable at a phospholipid dose of at least 100 mg/kg in 3-5 ml/kg saline. Natural surfactant or a third-generation synthetic surfactant should be used and the dosage repeated every 6 hours until oxygenation has improved [5, 23].

The surfactant is delivered directly into the airway in divided aliquots through an endotracheal tube or by infusion through a sidehole adapter. Surprisingly, bolus administration probably gives better distribution than intratracheal infusions [24]. If an infant has responded to the first dose and has subsequently deteriorated, a second dose should be seriously considered, even if the recommended time gap has not yet elapsed, and even if the chest radiograph indicates relatively well-expanded lung fields. Aerosolization of surfactant and continuous positive airway pressure assisted delivery of surfactant have been studied as a means to deliver surfactant to the lungs without the need for intubation. These techniques have not yet been proven to be effective.

Role of surfactant therapy in MAS:

Surfactant therapy can partially reverse the surfactant inactivation and thereby improve lung function. The limited data from controlled clinical trials indicate that surfactant therapy involving instillation or lavage reduces the need for extracorporeal life support (ECLS) in infants with MAS.

Bolus surfactant therapy has been found to improve oxygenation [6, 7] with reduction in the severity of respiratory distress and decrease in the number of infants with progressive respiratory failure requiring ECMO. Repeat intermittent bolus of high-dose surfactant has been found to improve oxygenation; resolve persistent pulmonary hypertension; and decrease the number of air leaks, need for extra- corporeal membrane oxygenation, and the duration of mechanical ventilation [25, 26]. It also shows an appreciable improvement in pneumothorax and decrease in mortality [27, 28]. However no significant decrease in pulmonary interstitial emphysema or chronic lung disease is achieved [29]. Emerging evidences support the use of bolus surfactant therapy on a case by case basis in neonatal care units, with a relatively high mortality associated with MAS, or where there is lack of availability of other forms of respiratory support such as high-frequency ventilation or nitric oxide.

Lung lavage with diluted surfactant has been proposed as a safe [27] alternative method of surfactant use for MAS. These basically enhance the removal of surfactant inhibitors from the alveoli and thus augment surfactant function [30]. It has been reported that lung lavage with dilute surfactant (Survanta) in ventilated infants with severe MAS does not decrease the duration of respiratory support, but may produce a reduction in mortality, especially in units not offering ECMO [31].

Unlike RDS treatment, where even a single dose is sufficient to help improve oxygenation dramatically and allow safe extubation thereafter, in MAS sustained improvement in oxygenation is seen only after at least the second bolus, necessitating the repeat of doses 6 hours apart to circumvent ongoing surfactant inactivation in infants who have MAS.

Monitoring of vitals:

During the administration of exogenous surfactant, heart rate, color, chest expansion, oximeter and endotracheal tube patency require diligent and meticulous monitoring during the first 30 minutes and compensate for acute changes in compliance or hemodynamics, if any. If surfactant

is being administered by infusion and the heart rate slows down or oxygen saturation falls more than 15%, dosing should be titrated down or stopped. The baby should be carefully evaluated clinically to establish the cause of the deterioration. If chest expansion improves substantially after dosing, peak ventilator inspiratory pressures should be reduced immediately, failure or delay to accomplish which can result in lung overdistention and pulmonary air leak.

Adverse effect and complications:

Among the notable adverse effects of surfactant administration are cardiorespiratory or mechanical [28]. In some infants, acute bradycardia or even cardiac arrest develops. Pulmonary hemorrhage, intraventricular hemorrhage, clinically significant PDA and transient suppression of the electroencephalogram are rare complications of surfactant administration [32]. Sometimes, the endotracheal tube may get blocked with surfactant. In such cases it is necessary to clear such a blockage urgently, or even to change the endotracheal tube. Intubation of the right main bronchus can result in delivery of the surfactant to the right side only, and this can cause overexpansion of the right lung and atelectasis of the left lung. No sensitivity to bovine surfactant and serum proteins has so far been reported.

Challenges:

Further analyses still need to be done to ascertain the optimal method of administration (lavage or bolus), preparation (bovine, porcine or peptide-containing synthetic preparation), dosing, and the time in the course of the disease when surfactant should be given. These may further be defined by the baseline severity of MAS in order to evaluate how these factors influence the effect of intervention. Supplementary trials that compare different combinations of volumes, concentrations, and methods of delivery need to be done. The efficacy of other approaches such as combined use of surfactant lavage with bolus remains to be determined. Potential benefit of the addition of polymyxin B or different polymers such as dextran hyaluronan or polyethyleneglycol, to surfactant preparations has also been studied by several groups to improve oxygenation or compliance as compared with surfactant alone.

Safety concerns regarding use of surfactant therapy largely remains to be investigated and addressed. Long-term prognostic indicators such as reduction in neurological sequelae and chronic lung disease should be further assessed.

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