

Surfactant therapy in late preterm infants

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Proceedings

Proceedings of the 9th International Workshop on Neonatology · Cagliari (Italy) · October 23rd-26th, 2013 ·
Learned lessons, changing practice and cutting-edge research

Abstract

Late preterm (LPT) neonates are at a high risk for respiratory distress soon after birth due to respiratory distress syndrome (RDS), transient tachypnea of the newborn, persistent pulmonary hypertension, and pneumonia along with an increased need for surfactant replacement therapy, continuous positive airway pressure, and ventilator support when compared with the term neonates. In the past, studies on outcomes of infants with respiratory distress have primarily focused on extremely premature infants, leading to a gap in knowledge and understanding of the developmental biology and mechanism of pulmonary diseases in LPT neonates. Surfactant deficiency is the most frequent etiology of RDS in very preterm and moderately preterm infants, while cesarean section and lung infection play major roles in RDS development in LPT infants. The clinical presentation and the response to surfactant therapy in LPT infants may be different than that seen in very preterm infants. Incidence of pneumonia and occurrence of pneumothorax are significantly higher in LPT and term infants. High rates of pneumonia in these infants may result in direct injury to the type II alveolar cells of the lung with decreasing synthesis, release, and processing of surfactant. Increased permeability of the alveolar capillary membrane to both fluid and solutes is known to result in entry of plasma proteins into the alveolar hypophase, further inhibiting the surface properties of surfactant. However, the oxygenation index value do not change dramatically after ventilation or surfactant administration in LPT infants with RDS compared to very preterm infants. These finding may indicate a different pathogenesis of RDS in late preterm and term infants. In conclusion, surfactant therapy may be of significant benefit in LPT infants with serious respiratory failure secondary to a number of insults. However, optimal timing and dose of administration are not so clear in this group. Additional randomized, controlled studies and evidence-based guidelines are needed for optimal surfactant therapy in these infants.

Keywords

Late preterm neonates, respiratory distress syndrome, pneumonia, pathogenesis, surfactant, ventilator therapy.

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How to cite

Yurdakök M. Surfactant therapy in late preterm infants. *J Pediatr Neonat Individual Med.* 2013;2(2):e020219. doi: 10.7363/020219.

Introduction

Prematurity, defined as birth before 37 weeks of gestation, is a major determinant of morbidity and mortality in newborn infants. A subset of premature neonates born between 34⁰/₇ and 36⁶/₇ weeks of gestation, classified as late preterm (LPT), account for 75% of preterm deliveries [1].

The preterm birth rate rose by more than 20 percent in the United States between 1996 and 2006. LPT neonates make up the fastest growing subset of premature infants, and there has been a 25% increase in their incidence over the last two decades. Rates rose for each gestational week from 34 to 36 weeks, with the largest increases for LPT births delivered at 36 weeks [2-5]. This increase might be due to a perception that electively delivered LPT babies face few risks.

The increase in incidence of LPT deliveries is due to multiple factors, such as increasing mean age of childbearing mothers, changes in infertility treatments, and an increasing incidence of multiple-gestation pregnancies [6-9]. Although it is not possible to know whether an infant would be born LPT, the increasing use of induction of labor and cesarean delivery at 34-36 weeks has influenced the upswing in the LPT birth rate [10-12]. The primary strategy for decreasing the rate of LPT birth must revolve around understanding the indications for these deliveries. Indicated deliveries included delivery for severe pre-eclampsia, intrauterine growth restriction with abnormal testing, or acute abruption. However, the group of "indicated" LPT births includes some deliveries for what are considered "soft" indications as "nonspontaneous, nonindicated" deliveries because it is unclear whether these deliveries are considered elective.

Many of the hypertensive disorders of pregnancy, excluding severe preeclampsia, are delivered in the LPT period without evidence to support this practice. Other soft indications for delivery include oligohydramnios, repeated cesarean, and dichorionic twin gestation [13]. Current evidence-based knowledge does not allow a safe reduction in LPT births [14].

Although the risk of early death and life-long morbidity in infants born LPT is low, infants born LPT are less healthy than infants born later in pregnancy. These neonates are at increased risk for hypothermia, feeding difficulties, hypoglycemia, hyperbilirubinemia, respiratory distress, intraventricular hemorrhage, necrotizing enterocolitis, and sepsis [15-17]. Ten to 33 percent of LPT infants are admitted to the NICU [1], require intensive and prolonged hospitalization [18, 19], and rehospitalisation after birth hospitalisation [20]. Mortality within the first year of life with 3- to 6-fold increased risk of death than term infants [19, 21] and brain injury that can result in long-term neurodevelopmental problems are high [22].

Respiratory distress syndrome

LPT neonates are at a high risk for respiratory distress soon after birth due to respiratory distress syndrome (RDS), transient tachypnea of the newborn, persistent pulmonary hypertension, and pneumonia, and along with an increased need for surfactant replacement therapy, continuous positive airway pressure, and ventilator support when compared with the term neonates [15, 23-27].

In the past, studies on outcomes of infants with respiratory distress have primarily focused on extremely premature infants, leading to a gap in knowledge and understanding of the developmental biology and mechanism of pulmonary diseases in LPT neonates. Surfactant deficiency is the most frequent etiology of RDS in very preterm and moderately preterm infants, while cesarean section and lung infection play major roles in RDS development in late preterm and term infants [28].

Pregnancies that undergo an indicated LPT delivery are more likely to be delivered via cesarean than by labor induction, leading to increased rates of respiratory compromise [3]. Neonates born by cesarean section have a larger residual volume of lung fluid and secrete less surfactant to the alveolar surface; thus, they are at higher risk of developing RDS. The process of labor is considered beneficial to the increased intrapulmonary fluid absorption and

the maturation and secretion of surfactant triggered by beta-adrenergic agents and prostaglandins [29]. Detrimental effect of cesarean section without labour on the development of RDS is more prominent in LPT and term infants [28, 30]. The relatively immature structural units of the respiratory tract in the LPT infant may be associated with delayed intrapulmonary fluid absorption, surfactant deficiency leading to inefficient gas exchange, and increased incidence of early respiratory morbidity.

Antenatal corticosteroid treatment

There is well-established evidence that antenatal corticosteroid treatment is effective for RDS prevention in preterm infants [31]. Antenatal corticosteroids are not routinely administered to pregnant women at risk for delivery between 34 and 36 6/7 weeks. However, antenatal corticosteroids stimulate the transcriptional activation of sodium channel subunits that are responsible for the effectiveness of intra-alveolar liquid resorption, as well as for the maturation of alveolar surfactant [29]. There are small studies showing administration of antenatal corticosteroids to patients at risk of imminent delivery 34-36 weeks could significantly reduce the acute respiratory morbidity associated with LPT birth [32-35]. It is, therefore, difficult to make any conclusions without large prospective studies on the use of glucocorticoids in pregnant mothers past 34 weeks of pregnancy [32, 36, 37].

Surfactant therapy

The clinical presentation and the response to surfactant therapy in LPT infants may be different than that seen in very preterm infants. Incidence of pneumonia and occurrence of pneumothorax are significantly higher in LPT and term infants. High rates of chorioamnionitis and pneumonia in LPT and term infants may result in direct injury to the type II alveolar cells of the lung, decreasing synthesis, release, and processing of surfactant [38]. Increased permeability of the alveolar capillary membrane to both fluid and solutes is known to result in entry of plasma into the alveolar hypophase, further inhibiting the surface properties of surfactant [39].

With lung injury as in pneumonia, an early response is the release of TNF- α and IL-1 β from macrophages. Neutrophils and endothelial cells are activated. Neutrophil sequestration in the alveolar capillaries and interaction with other inflammatory cells, such as monocytes,

macrophages, and lymphocytes, result. Platelet activation of neutrophils via release of their stored mediators, including von Willebrand factor, tissue factor, chemokines, and cytokines, is part of the response. In addition, cytokines, chemokines, acute-phase reactants, and coagulation factors are released from injured tissues, including TNF- α , IL-1, IL-6, and IL-8. These inflammatory substances damage the epithelium, increased permeability of the microvasculature, impair the alveolar-capillary barrier, cause plasma leakage into the alveolar space which can inactivate surfactant [40].

The major surfactant inhibitory factors in plasma are proteins (albumin, fibrinogen, and haemoglobin), and lipids (unsaturated membrane phospholipids, lysophospholipids, free fatty acids, supraphysiological levels of cholesterol). Surfactant inhibition can also arise from degradation of surfactant lipids by phospholipases or of surfactant proteins by proteases. These degradative agents, normally present in the alveolus at very low levels, can be increased during microbial infection and more importantly through secretion by leukocytes and type II cells with pulmonary inflammation, particularly during acute lung injury and RDS [41].

Reduced production and increased inactivation causes secondary surfactant deficiency in pneumonia. Therefore in severe cases with pneumonia, surfactant therapy may be necessary to improve oxygenation and ventilation [42-45]. However, the oxygenation index value do not change dramatically after ventilation or surfactant administration in LPT infants with RDS compared to very preterm infants. These finding may indicate a different pathogenesis of RDS in LPT and term infants [28].

Because of that early and severe RDS develop in these infants. It is more likely to lead to the development of persistent pulmonary hypertension and multiple organ system failure (MOSF), especially involving myocardial injury and acute renal failure. Most neonates with this condition require prolonged mechanical ventilation and continuous positive airway pressure (CPAP), ranging from 10 to 14 days, correspondingly, there is a higher incidence of pneumothorax. The mortality rate remains relatively high for these infants which is most often related to severe infection complicated by MOSF [28, 46].

Conclusions

In conclusion, surfactant therapy may be of significant benefit in LPT infants with serious

respiratory failure secondary to a number of insults. However, optimal timing and dose of administration are not so clear in this group. Additional randomized, controlled studies and evidence-based guidelines are needed for optimal surfactant therapy in these infants [42].

Declaration of interest

The Author declares that there is no conflict of interest.

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