Preterm infants: is prophylactic surfactant therapy and early vitamin A supplementation the way ahead?

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The neonatal mortality rate (NMR) in India (as per UNICEF) is 34/1000 live births, whereas in tertiary care centres of the Armed Forces Medical Service (AFMS), it ranges between 12 and 25/1000 (unpublished data). On an average 2.7 million preterm live births are recorded in this country every year. Respiratory distress syndrome (RDS) is the single most important cause of morbidity and mortality worldwide in preterm infants.¹ Prematurity is also associated with low stores of micronutrients at birth and thereby preterm neonates are at increased risk of developing effects of vitamin deficiencies. It is in this context that the two studies appearing in this issue of the journal on role of prophylactic surfactant in preterm infants and umbilical cord blood vitamin A levels in low birth weight babies, focus on further reducing neonatal mortality and morbidity in AFMS Hospitals.^{2,3}

RESPIRATORY DISTRESS SYNDROME

Avery and Mead in 1959 first demonstrated that lungs of infants with RDS were poorly compliant due to surfactant deficiency. RDS, earlier called hyaline membrane disease, is a syndrome in premature infants caused by developmental insufficiency of surfactant production and structural immaturity of the lungs. The incidence decreases with advancing gestational age, from about 50% in babies born at 26–28 weeks, to about 25% at 30–31 weeks. Most newborns destined to develop RDS appear normal at birth. The first symptom usually appearing within an hour of birth is increased respiratory effort with intercostal retractions and the use of accessory muscles of respiration. The respiratory rate may increase to more than 100 breaths/min and the baby becomes cyanotic.

The lungs of infants with RDS are developmentally deficient in surfactant, a lipoprotein complex which prevents collapse of the alveoli throughout the respiratory cycle by reducing surface tension of the fluid that lines the alveoli. As a result of surfactant deficiency respiratory failure ensues resulting in hypoxia and acidosis. The diagnosis is made by the clinical picture and the chest X-ray, which demonstrates decreased lung volumes, a small, discrete, uniform infiltrate that involves all lobes of the lung (described as a “ground glass” appearance), and the presence of air-bronchograms.

Most cases of infant respiratory distress syndrome can be prevented if mothers are given glucocorticoids during the antenatal period. The American College of Obstetricians and Gynecologists (ACOG) have recommended antenatal glucocorticoid treatment for women at risk for preterm delivery prior to 34 weeks of gestation.⁴

Role of Prophylactic Surfactant

The first successful trial of surfactant treatment for RDS was reported in 1980. Since then there have been numerous randomised trials demonstrating firstly, the efficacy of surfactant treatment and increasing survival, and secondly assessing various other aspects of surfactant therapy. Both prophylactic and early surfactant replacement therapy in a select group of neonates born at less than 32 weeks of gestation have been shown to decrease mortality by more than a third and markedly reduce the complications of ventilation like pneumothorax, pulmonary interstitial emphysema and bronchopulmonary dysplasia (BPD) compared with later selective surfactant administration.^{5–8} Natural surfactants are more effective than synthetic products, the latter now being used infrequently. Early surfactant replacement therapy, extubation, followed by nasal continuous positive airway pressure (nCPAP) ventilation, i.e. INSURE (IntubationSURfactantExtubation), when compared with later selective surfactant replacement and continued mechanical ventilation, leads to a reduced need for mechanical ventilation, lower incidence of BPD and fewer air leak syndromes.^{9,10} The CURPAP study, an international randomised controlled trial, also tried to evaluate the efficacy of combining prophylactic surfactant and early nCPAP in very preterm infants. However, prophylactic surfactant was not found to be superior to nCPAP and early selective surfactant in decreasing the need for mechanical ventilation in the first five days of life in spontaneously breathing very preterm infants on nCPAP. In addition, the incidence of main morbidities of prematurity was not affected.^{11,12} The last 25 years have also seen a major thrust in basic research on the structure and function of four surfactant proteins. Future studies will focus on widening the indications for surfactant treatment, developing non-invasive means of administration and assessing the value of newer synthetic surfactants.

Role of Vitamin A in Preterm Babies

Full-term neonates are born with marginal reserves of vitamin A and depend on breast milk or other sources to meet their metabolic demands in the first few months of life. Premature infants have even lower reserves of vitamin A and correction

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of the deficiency has been shown to reduce the respiratory complications of preterm birth.^{13,14}

A study in 1999 suggested that mild vitamin A deficiency delays fetal lung maturation in the rat, which led to the investigation of a new approach for prevention of RDS.¹⁵ Vitamin A is systemically bio-available after intratracheal administration along with surfactant in an animal model of newborn respiratory distress,¹⁶ and surface activity of surfactant is spiked when co-administered with vitamin A in vitro.¹⁷ This fact has revived interest in prophylactic vitamin A therapy, which was largely hitherto for being used to prevent chronic lung disease in extremely low birth weight babies.

It is well known that vitamin A deficiency predisposes infants and children to frequent respiratory tract and gastrointestinal tract infections. Current guidelines recommend an intake of 700–1500 IU/Kg/day vitamin A, and there is evidence to support higher doses for infants with significant lung disease. The importance of appropriate early nutrition for preterm infants is apparent, however, recommendations for intravenous vitamin A supplementation for parenterally fed preterm infants require revision. Intravenous lipid with added fat soluble vitamins should be started as soon as possible after birth, and consideration given to early oral vitamin A supplementation in those infants tolerant of enteral feeds.¹⁸

The prophylactic use of surfactant in preterm infants and the use of cord blood vitamin A levels to indicate the need for its supplementation in low birth weight babies, both are still controversial and require further trials before change in protocols can be recommended.

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