Surfactants in Newborns

Dr. King-woon So
Dr. Simon H Lam
Prof. Pak-cheung Ng
Department of Paediatrics, Prince of Wales Hospital,
The Chinese University of Hong Kong

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 August 2005.

Surfactants (an abbreviation of “surface active agent”) are substances that lower the surface tension of the fluid they are adsorbed or dissolved in, thereby enabling it to spread over surfaces more readily. This characteristic plays a crucial role in pulmonary physiology. Alveolar type II epithelial cells of the lungs produce pulmonary surfactant which by decreasing surface tension in the alveoli, counteracts the tendency of lung tissue to collapse and stabilises the lung volume at low trans-pulmonary pressures.1

Natural pulmonary surfactant comprises approximately 80% phospholipids, 8% neutral lipids, and 12% protein. One of the components crucial in reducing surface tension is dipalmitoylphosphatidylcholine (DPPC). This is an amphipathic molecule with a polar hydrophilic head and a non-polar hydrophobic tail. The amphipathic nature of DPPC allows it to be adsorbed at the pulmonary air/liquid interface and reduces the tendency of alveolar collapse. Four unique surfactant-associated proteins have been identified: SP-A, SP-B, SP-C, and SP-D.2,3 Recent studies show that these proteins play important roles in: (i) maintenance of a lipid monolayer at the air-liquid interface,4 (ii) regulation of surfactant protein synthesis,5 (iii) modification of the inhibitory effect of plasma proteins on surfactant,6 and (iv) involvement in the host immune response against invading pathogens.7

Although Avery and Mead first described the abnormal surface activity of lung extracts in preterm infants who had died of respiratory distress syndrome (RDS) in 1959,8 it was not until 1980 that Fujiwara et al reported the successful use of surfactant replacement therapy in human infants with RDS.9 Thereafter, many randomised controlled trials have been conducted to determine the type, timing, and dosage of surfactant that should be used in preterm infants.

Several types of surfactant are available on the market for clinical use. These can be broadly classified into the synthetic surfactants, such as Exosurf (colfosceril palmitate, Glaxo Wellcome Inc., Research Triangle Park, N.C., U.S.A.), and the natural surfactants, such as Survanta (beractant, Ross Laboratories, Columbus, Ohio, U.S.A.), Infasurf (calf lung surfactant extract, ONY Inc., Amherst, N.Y., U.S.A.), and Carusurf (poractant alfa, Chiesi Farmaceutici, Parma, Italy). Both groups of surfactant have been shown to be effective in reducing airleak syndromes, bronchopulmonary dysplasia (BPD), and mortality in preterm infants with RDS.10 Synthetic surfactants, which do not contain any active biological components, have slower onset of action, but carry no risk of disease transmission. In contrast, natural surfactants contain surfactant proteins such as SP-B and SP-C, and are able to produce rapid improvements in lung compliance. The latter preparations are also less sensitive to inhibition by serum proteins.11 A meta-analysis revealed that the use of natural surfactants in preterm infants with RDS was associated with earlier pulmonary improvement, fewer pneumothoraces, and a reduction in mortality compared with the synthetic preparations.12

Surfactants can be used prophylactically or therapeutically. Prophylactic administration implies the universal replacement of surfactant for infants born before a certain pre-defined gestational age, such as 30 weeks, disregarding the presence or absence of RDS. Therapeutic administration is where only preterm infants fulfilling pre-defined clinical and radiological criteria are given surfactant replacement. A recent meta-analysis comprising 8 randomised controlled trials comparing prophylactic versus therapeutic surfactant administration suggested that prophylactic treatment was associated with a decrease in the incidence of pneumothoraces, pulmonary interstitial emphysema, BPD, and mortality.13 Despite these advantages, prophylactic administration of surfactant immediately after birth is still not routine practice in most centres in Hong Kong. The rationale is that most neonatologists consider that the neonatal intensive care unit (NICU) is a better environment than the labour ward for providing essential monitoring during the intervention, especially if the NICU is in close proximity to the labour ward.14 If therapeutic treatment is practised, early treatment within 2 hours of birth is preferred, as this has been shown to reduce the risk of airleak syndrome, BPD and mortality compared with delayed treatment.15

Treating RDS with either one or multiple doses of surfactant has major financial implications. From early series of surfactant replacement trials, approximately one third of treated infants relapsed after the initial dose and many required further doses.16 A meta-analysis subsequently showed that the use of multiple doses resulted in more sustained improvements in oxygenation, a reduction in the requirement for ventilatory support, and decrease in the
incidence of pneumothoraces. The timing, number of doses, and the optimal clinical criteria for giving additional doses, however, remained undetermined. Speer and colleagues suggested using Curosurf 200 mg/kg as the initial dose, with a second and third dose each at 100 mg/kg at 12 and 24 hours after delivery if the infant still required oxygen supplementation and mechanical ventilation. Dunn et al suggested to use bovine surfactant at 100 mg/kg doses. After the first dose, the criteria for further treatment were: (i) a positive response to the first dose (a decrease in FIO₂ down to 0.21 or by > 0.1) and (ii) a subsequent respiratory deterioration (as evidenced by an increase in FIO₂ by ≥ 0.1) that was not associated with a pneumothorax. In this study 70% of patients received a second dose, 41% received a third dose, and 11% received a fourth dose. While 30% of infants would need only one dose of surfactant, 41% would require more than 2 doses if this “threshold” regimen were adopted. Thus, the commonly adopted two-dose regimen may not satisfy the needs of the individual patient and the drug regimen should be tailored according to the clinical status after the initial dose. Current reviews are already looking at differences on respiratory outcomes, mortality and resource utilisation of high versus low thresholds for administration of subsequent doses of surfactant. Intubation and initiation of mechanical ventilation as opposed to early and routine use of non-invasive ventilation such as nasal continuous positive airway pressure (nCPAP) are important risk factors associated with the development of BPD in very low birthweight infants. Early surfactant administration followed by extubation to nCPAP (INSURE regime: intubation, surfactant administration, and then rapid extubation to nCPAP) has been used to reduce the use of mechanical ventilation and the incidence of BPD in preterm infants with RDS. A meta-analysis of 4 randomised controlled trials showed that early surfactant replacement followed by nCPAP reduced the need for subsequent mechanical ventilation by 30% in patients with RDS. Although aerosolisation is a gentler method for delivering surfactant to the lung (as intubation is not required), it has been shown to be less effective than direct tracheal instillation and requires a much greater volume of the drug. Further, no beneficial effects could be demonstrated by giving aerosolised surfactant to infants receiving nCPAP in a pilot study. Intubation for surfactant administration is still necessary in regimes using early nCPAP. Apart from preterm infants with RDS, infants with other pathological pulmonary conditions affecting the production and function of surfactant may also benefit from exogenous surfactant replacement therapy. Meconium aspiration syndrome (MAS) occurs in 1% to 5% of near-term liveborn deliveries. Meconium comprising cholesterol, free fatty acids, bilirubin, and plasma protein, inactivates surfactants. It also activates alveolar macrophages and induced inflammation. Both animal and human studies have demonstrated that high dose surfactant replacement therapy (e.g. Surfactant 150 mg/kg/dose given 6 hourly up to 4 doses) could ameliorate the inhibitory effect of meconium, thereby improving lung compliance and oxygenation. A meta-analysis also showed that natural surfactant replacement in term infants with MAS reduced the severity of respiratory illness, and decreased the number of infants that developed progressive respiratory failure requiring extracorporeal membrane oxygenation (ECMO). However, no effect on mortality could be demonstrated. Lipopolysaccharides produced by pneumonic pathogens and the inflammatory cytokines produced during infection or inflammation can downregulate surfactant protein production. This results in worsening of pulmonary compliance. Infants with congenital pneumonia can, therefore, have disturbances in alveolar surface tension similar to preterm infants suffering from RDS, despite an elevated lecithin/sphingomyelin ratio. Infection is a cause of surfactant dysfunction. A retrospective study of surfactant treatment for infants with respiratory failure secondary to infection demonstrated that significant improvement in oxygenation occurred within one hour of treatment. Compared to patients with RDS, the response of infected infants was slower and repeated doses were more often required. A subgroup analysis of infants with pneumonia in a randomised controlled study suggested that surfactant therapy significantly improved oxygenation and reduced the need for ECMO by 40%. Surfactant may also have a role in the treatment of infants with BPD. Surface tension of bronchial lavage specimens obtained from infants with BPD was noted to be as high as specimens obtained from infants with inherited SP-B deficiency. Further, deterioration in the respiratory status of preterm infants ventilated beyond one week was associated with a reduction in SP-B content and surfactant dysfunction. Surfactant replacement therapy in infants with early BPD resulted in improvement in oxygenation and ventilation, though these beneficial effects could not be sustained beyond 72 hours. The long-term benefits of using surfactant in the treatment of BPD, especially in relation to shortening the duration of ventilation and reducing mortality, remains to be evaluated. Amniotic fluid of infants with congenital diaphragmatic hernia (CDH) has been shown to have lower lecithin/sphingomyelin ratios and SP-A content compared with normal infants. Animal and uncontrolled human studies have shown that surfactant replacement therapy could improve oxygenation and ventilation in newborns with CDH. However, Lotze et al failed to show any benefit of surfactant therapy in infants who were already receiving ECMO. In summary, surfactant therapy reduces mortality and respiratory morbidity in preterm infants with RDS. Early administration of surfactant together with non-invasive respiratory support can reduce the requirement for intubation and may decrease the chance of development of BPD. Clinical conditions that can interfere with surfactant synthesis and recycling such as pneumonia and MAS may also be benefited from surfactant therapy. Nonetheless, the optimal dosage and the most appropriate method of delivery for these different conditions are still controversial and further investigation is warranted.

References

1. Jobe AH. Pulmonary surfactant therapy. NEJM 1993; 328: 961-68

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Medical Bulletin
10. Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. The Cochrane Library Volume (4) 2004 (Soll RF. Prophylactic natural surfactant for preventing morbidity and mortality in preterm infants. The Cochrane Library Volume (4) 2004
12. Soll RF, Bianco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. The Cochrane Library Volume (4) 2004
13. Soll RF. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. The Cochrane Library Issue (4) 2004
15. Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. The Cochrane Library Volume (4) 2004
17. Soll RF. Multiple versus single dose natural surfactant extract for severe neonatal respiratory distress syndrome. The Cochrane Library Volume (4) 2004
19. McCully TJ, Suresh GC, Soll RF. High versus low thoracic pressures for repeated administration of surfactant in premature neonates. The Cochrane Library Volume (4) 2004
22. Stevens TP, Renzow M, Soll RF. Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with respiratory distress syndrome. The Cochrane Library Volume (4) 2004
28. Soll RF, Dargaville P. Surfactant for meconium aspiration syndrome in term infants. The Cochrane Library Volume (4) 2004

MCHK CME Programme Self-assessment Questions

Please read the article entitled “Surfactant in Newborns” by Dr. King-woon So, Dr. Simon H Lam and Prof. Pak-chung Ng and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheet via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 August 2005. Answers to questions will be provided in the next issue of The Hong Kong Medical Journal.

Questions 1- 10: Please choose the best answer or T(True) or F(False).

1) Functions of surfactant proteins include:
   a. regulation of surfactant proteins synthesis
   b. modification of the inhibitory effect of plasma proteins on surfactants
   c. maintenance of the lipid monolayer at the air-liquid interface
   d. involvement in the immune response to invading pathogens
   e. all of the above

2) Natural surfactants carry no risk of disease transmission because they do not contain biologically active surfactant protein. T / F

3) A meta-analysis comparing natural surfactants with synthetic surfactant for treatment of respiratory distress syndrome in preterm infants showed:
   a. treatment with synthetic surfactant resulted in more rapid pulmonary improvement compared with natural surfactant
   b. treatment with synthetic surfactant resulted in a decrease in the incidence of bronchopulmonary dysplasia
   c. treatment with natural surfactant resulted in less necrotising enterocolitis
   d. treatment with natural surfactant resulted in reduced mortality
   e. treatment with synthetic surfactant resulted in fewer pneumothoraces

4) Prophylactic administration of surfactant for preterm infants refers to surfactant replacement therapy immediately after birth even if the infants do not have respiratory distress syndrome. T / F

5) According to a Hospital Authority (HA) survey in 2000, prophylactic administration of surfactant to preterm infants in the labour ward is routine practice at all HA hospitals in Hong Kong. T / F
6) For therapeutic administration of surfactant for respiratory distress syndrome in preterm infants, the first dose of surfactant is best given:
   a. within 2 hours after delivery
   b. within 4 hours after delivery
   c. within 8 hours after delivery
   d. within 12 hours after delivery
   e. within 24 hours after delivery

7) A meta-analysis comparing a single dose with multiple doses of surfactant for treatment of respiratory distress syndrome in preterm infants showed that:
   a. multiple doses reduced mortality
   b. multiple doses reduced subsequent development of patent ductus arteriosus
   c. multiple doses resulted in a more sustained improvement in oxygenation
   d. multiple doses increased the risk of pneumothorax
   e. multiple doses reduced the risk of retinopathy of prematurity

8) Early surfactant replacement with aggressive use of nCPAP can reduce the need for subsequent intubation and mechanical ventilation in preterm infants with RDS. T / F

9) Which of the following statements is incorrect?
   a. Meconium inactivates surfactant by its components, which include cholesterol, free fatty acids, bilirubin and plasma proteins
   b. Surfactant replacement therapy reduces mortality in newborns with meconium aspiration syndrome
   c. Surfactant function can be inhibited by lipopolysaccharides and inflammatory cytokines in patients with pneumonia
   d. Surfactant replacement therapy can reduce the need for ECMO in infants with respiratory failure due to pneumonia
   e. Surfactant replacement therapy in infants with early chronic lung disease results in improvement of oxygenation

10) Amniotic fluid from infants with congenital diaphragmatic hernia has higher lecithin/sphingomyelin ratio and SP-C content compared to normal infants. T / F

ANSWER SHEET FOR AUGUST 2005
Please return the completed answer sheet to the Federation Secretariat on or before 31 August 2005 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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Dr. King-woon So, Dr. Simon H Lam and Prof. Pak-cheung Ng
Department of Paediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong

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Answers to July 2005 issue
Phosphodiesterase Type 5 (PDE5) Inhibitors for the Treatment of Erectile Dysfunction: A Comparison