Paediatrica Indonesiana

VOLUME 45 November - December • 2005 NUMBER 11-12

Review Article

Use of surfactant in neonatal intensive care units

M Sholeh Kosim

Surfactant is currently an important therapy for newborns in neonatal intensive care units (NICUs) with respiratory problems, specifically respiratory distress syndrome (RDS). Surfactant was initially used in 1959, after it was recognized for maintaining lung inflation at low transpulmonary pressures. Avery and Mead in Jobe[1] reported that saline extracts from the lungs of preterm infants with RDS lacked the low surface tension characteristics of pulmonary surfactant. Subsequently, in 1980, clinical potential of surfactant therapy for RDS was demonstrated by Fujiwara *et al*, reported in Jobe,[1] in the use of surfactant prepared from an organic solvent extracted from bovine lung (Surfactant TA). Small randomized controlled trials (RCTs) in 1985, which tested surfactants prepared from bovine alveolar-lavage or human amniotic fluid, demonstrated significant decrease in pneumothorax and death rates. Subsequent multi-center trials demonstrated decreased death rates and complications of RDS; although still investigational, its use begun in 1989. A synthetic surfactant was approved for the treatment of the syndrome in the United States in 1990, and an animal surfactant was approved in 1991. These surfactants represent a new class of drug developed specifically for preterm infants.[1]

Characteristics of surfactant

Surfactant is a complex substance containing phospholipids and a number of apoproteins. This essential fluid is produced by the Type II alveolar cells which lines the alveoli and smallest bronchioles. Surfactant reduces surface tension throughout the lung, thereby contributing to its general compliance. It is also important because it stabilizes the alveoli. Surfactant is formed relatively late in fetal life; thus premature infants born without an adequate amount of it experience respiratory distress and may die.[2]

Endogenous surfactant, normally produced by type II alveolar epithelial cells within the lung, is primarily responsible for the prevention or reduction of alveolar collapse due to an increase in surface tension within the alveoli. Because the process of surfactant production takes place relatively late in fetal life (from 22 to 24 weeks gestation throughout 32 weeks gestation), infants born prematurely are at risk for surfactant deficiency. This deficiency results in the development of RDS, also known as hyaline membrane disease (HMD).[3]

Types of surfactant

Pulmonary surfactant is a complex mixture of lipids and specific apoproteins, 80% phospholipids, 8% neutral lipids, and 10-12% proteins. The phospholipid

Presented in the 2nd National Congress of Perdici (Indonesian Society of Intensive Care Medicine), Semarang, Indonesia on June 25, 2005.

From the Department of Child Health, Medical School, Diponegoro University, Kariadi Hospital, Semarang, Indonesia.

Reprint requests to: M Sholeh Kosim, Perinatology Division, Department of Child Health, Medical School, Diponegoro University, Kariadi Hospital, Semarang, Indonesia. Tel./Fax: 62-24-8414296, E-mail: mskosim@indosat.net.id

component consists of 60% saturated phosphatidylcholine (PC), 20% unsaturated PC and anionic phospholipids, phosphatidylglycerol (PG), and phosphatidylinosotol. The main active component is dipalmityl phosphotidylcholine (DPPC) which is responsible for reducing surface tension and maintaining alveolar stability, both animal and artificial surfactants are available in the market. The former, derived from bovine and porcine lungs, contains surfactant proteins B and C. It is more effective than artificial surfactant which lacks these surfactant proteins.[4] The Canadian Pediatrics Society recommends the use of natural surfactants in preference to any synthetic ones available.[5]

Pharmacokinetics of surfactant

Infants with RDS have pools of surfactant on the order of 5 mg per kilogram, whereas in newborn animals the pool is about 100 mg per kilogram. The usual dose of 100 mg per kilogram approximates the amount of surfactant in the air spaces of term newborn animals. However, much of this surfactant rapidly becomes lung associated and cannot be recovered by alveolar lavage.[1]

Indications for the use of surfactant

Neonatal surfactant deficiency states, especially HMD in premature infants, require surfactant treatment.[3,6] Surfactant is also used in neonatal lung injury not related to prematurity, such as congenital diaphragmatic hernia (before and after surgical repair) and meconium aspiration syndrome.[4,5] Other indications requiring surfactant for therapy are lung injury in neonates, infants, and children (inhalation syndrome, bacterial pneumonia, bronchiolitis), and adult respiratory distress syndrome (ARDS) which includes those of sepsis-induced, trauma, hypoxic respiratory failure, oncohematologic cases in children and adolescents.[4]

Risks of exogenous surfactant therapy

The short-term risks of surfactant replacement therapy, for example, are bradycardia, hypoxemia, and increase in pulmonary hemorrhage. Bradycardia, hypoxemia, and blockage of the endotracheal tube may occur during instillation. There is also a chance of increase in pulmonary hemorrhage following surfactant treatment. However, mortality ascribed to pulmonary hemorrhage is not increased and overall mortality is lower after surfactant therapy. The relative risk (RR) for pulmonary hemorrhage following surfactant treatment has been reported at approximately 1.47 (95% CI 1.05 to 2.07) in trials but, unfortunately, many of the RCTs on surfactant replacement have not reported this outcome, nor have the data from autopsy studies clearly defined the magnitude of this (evidence level 1a).[5]

As of yet, there is no evidence of immunological change which may influence clinical concern. Babies with RDS have detectable circulating immune complexes directed towards surfactant proteins, but these do not appear to be more frequent in babies are treated with surfactants.[4,5]

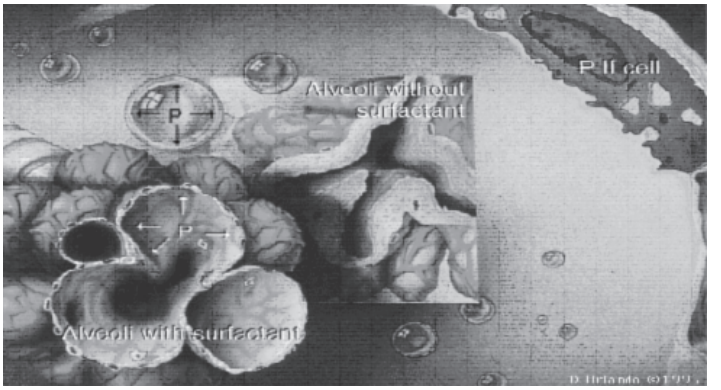

FIGURE 1. ALVEOLI WITH AND WITHOUT SURFACTANT[2]

Timing of surfactant treatment

Initially, surfactant was administered 6 to 24 hours after birth when diagnosis of severe RDS could be made accurately. In contrast, delivery-room treatment was considered to be optimal if given before the infant breathed or received positive-pressure ventilation (PPV). This delivery room strategy was based on information from surfactant treatment of preterm animals demonstrating airway epithelial damage with minimal ventilation of the surfactant-deficient lung. The two treatment strategies have been compared in three independent trials using different surfactants. The efficacy of the two strategies was similar in one trial that included 55 infants who were treated in the delivery room and 50 infants who were treated at a mean age of 3.7 hours.[1]

Retreatment should be considered when there is a persistent or recurrent oxygen requirement of 30% or more and it may be given as early as 2 hours after the initial dose or, more commonly, 4-6 hours after the initial dose.[5]

Clinical Implications

Circulatory Effects

A number of investigators have looked into the cardiovascular effects of surfactant therapy. It can be expected that surfactant will improve lung compliance which leads to a decrease in pulmonary vascular resistance and an increased pulmonary blood flow. The clinical observation of patent ductus arteriosus (PDA) following surfactant treatment was thought to be due to the drop in pulmonary vascular resistance (PVR). Although there is a demonstrable decrease in PVR and an increase in pulmonary artery pressure (PAP) and pulmonary blood flow and consequent development of PDA, there is decreasing incidence of PDA with better management suggesting surfactant per se is not the cause for the PDA.[6]

Increased incidence of PDA following surfactant therapy has been widely reported. A meta-analysis of 6117 infants from 28 studies showed no general increase in PDA after treatment.[6]

Cerebral circulation

Although some authors have reported a decrease in cerebral blood flow volume (CBFV), others showed an increased CBFV; however, there are no significant changes that occurred with surfactant therapy. Porcine surfactant decreases mean arterial blood pressure (MABP) by inducing vasodilation. The effect is dose dependant. This vasodilatation is inhibited by nitric oxide (NO) synthetase by LNAME with Curosurf MABP and left ventricular cardiac output increased about 29 percent; other studies did not show consistent results.[6]

Pulmonary functions

Pulmonary functions have been studied in infants treated with surfactant. In exosurf treated infants, compliance improved 24 hours after treatment; forced respiratory capacity (FRC) increased 12 hours after treatment. Improvement in oxygenation is not followed by improvement in compliance. The immediate improvement may be due to improvement in ventilation perfusion ratio.[4,6]

Renal function

The onset of spontaneous diuresis was evaluated in 19 infants with HMD, in a double-blind controlled study, 12 with surfactant and 7 as control. There was no difference in the time of onset for diuresis output of >80% intake. Glomerular filtration rate (GFR) was similar in the surfactant group and control group during the first 3 days of life. Ventilator status improved soon after surfactant therapy. Data suggested ventilatory status improvement was not due to diuresis. Other factors are thought to be responsible.[6]

Treatment response

Uniform improvement in oxygenation has been found after surfactant treatment. Some response may be poor due to existing acidosis from severe hypoxia or myocardial failure. In a small percentage, poor response may result from the presence of PDA. Infants with cyanotic congenital heart disease will show no response. An initial good response followed by reversal may result from inappropriate ventilatory management following

surfactant therapy (e.g. not changing peak pressure with subsequent development of pneumothorax).[8]

Role of surfactant in host defenses

Surfactant proteins A and D are being increasingly identified as important factors in host defense of lung. Surfactant protein A (SPA), binds and opsonizes bacteria, including group B *streptococcus, pseudomonas*, and *pneumococcus*. It agglutinates herpes and influenza virus, and attaches to lipoprotein synthesis (LPS) endotoxin. SPA deficient mice are susceptible to Group B Streptococcus (GBS) infection. SPA concentrations are low in lavage fluid from premature infants. It decreases by infection from RSV, bacteria, LPS and tumor necrosis factor-X (TNFX). SPA also activates macrophages and polymorphonucleocytes (PMNs), enhances destruction of bacteria. Surfactant protein D synthesized by bronchiolar, tracheal-bronchial and alveolar epithelial cells. It binds *E.coli, Salmonella, Klebsiella,* increasing the uptake and killing of bacteria. It also agglutinates virus, and binds with LPS. Concentrations in bronchi-alveolar lavage are low in prematurity. Thus, natural surfactant plays unknown roles that are very critical for the survival of immature infants.[6]

Administration of surfactant

Some points should be considered before surfactant installation, such as its administration. Direct instillation manages surfactant directly into the distal end of the tracheal tube via a premeasured bronchial suction catheter, or via nebulizer in ventilator gases. Direct instillation is less efficient and leads to surfactant loss in the endotracheal tube. The most uniform distribution of surfactant is by using a nebulizer during a brief period of manual ventilation (2-3 minutes), with respiratory physiotherapy and postural drainage. In Indonesia, such surfactant is not available. Administration of surfactant in 2-4 divided doses avoids early deterioration of gas exchange and unwanted vagal reflexes. The airways should not be suctioned for the first hour after surfactant administration.

Several studies have demonstrated the beneficial effects of applied positive end expiratory pressure (PEEP) in improving and sustaining the therapeutic effects of surfactant. Using a conventional tube has been suggested in selective bronchial instillation of surfactant which is presented in one main bronchus by a bilumen tube or bronchoscope. The advantages deriving from this method is the delivery of large doses to distal regions of the lung and the reduction of instilled dose (costs). The disadvantages are connected with the complexity of procedures and length of treatment.[4] To avoid adverse reactions, a sedative or pain reliever is sometimes needed.

Surfactant replacement therapy

Initial reports of significant improvement in the clinical course of infants with severe HMD, following the installation of surfactant, are most encouraging. Fujiwara, reported in Chernick,[7] instilled a liquid surfactant into the trachea of infants with HMD which was obtained from tracheal washings of cow lung and modified to exclude most of the protein (Fujisurf). The British have used a dry powder insufflation which consisted of a combination of dipalmitoyl lecithin and diacylphosphotidylglycerol (7:3 ratio, water/water). This approach is proven to be a major advance in our therapy of those infants with HMD whose lungs can not be matured *in utero*. Certainly, one might speculate that replacement therapy will succeed artificial ventilation as the therapy of choice in the future, thereby avoiding the serious complications associated with prolonged ventilation of these tiny infants.[7]

Horbar *et al*[9] conducted a study in NICUs involving 114 units which treated 6039 infants of 23-29 weeks gestation born in 2001. Results of this study revealed that compared to control hospitals, infants in intervention hospitals were more likely to receive surfactant in the delivery room [adjusted odds ratio 5.38 (95% CI 2.84 to 10.20)] were less likely to receive the first dose more than two hours after birth [adjusted odds ratio 0.35 (0.24 to 0.53)], and received the first dose of surfactant soon after birth (median of 21 minutes *vs* 78 minutes, $P<0.001$). The intervention effect on timing of surfactant was larger for infants born in the participating hospitals than for infants transferred to a participating hospital after birth. There were no significant differences in mortality or pneumothorax. Conclusion of this study was a multifaceted intervention including audit and feedback, evidence reviews, quality improvement training, and follow-up support which changed the behavior of health professionals and promoted evidence based practice.[9]

Narang *et al*[10] conducted another study on 207 babies with HMD requiring mechanical ventilation were admitted in NICU. Out of these, 88 babies received surfactant. Amongst those who received surfactant, 65% received one dose, 25% received two doses and 10% received three doses. The babies in both groups had comparable characteristics except for those delivered by Cesarean Section, which was significantly higher in the surfactant group. Conclusion of the study revealed that the use of surfactant improved the survival and decreased the associated morbidities in babies with HMD who required mechanical ventilation. The maximum impact was seen among the babies of 28-33 weeks gestation and birth weight group 1000-1249 grams. It has been shown that a single dose of surfactant at birth followed by continuous positive airway pressure (CPAP) significantly reduces the subsequent need for mechanical ventilation. Hence, it may be worth considering prophylactic surfactant therapy in high-risk neonates between 28-32 weeks gestation even in the absence of elaborate level III care setup in the country.[10]

Surfactant preparations

The exogenous surfactant preparations available currently are natural bovine lung extracts, surfactants obtained from the lavage of calf lungs, extracts of porcine lung surfactants, and synthetic preparations.

Administration of exogenous surfactant is considered an appropriate prophylactic treatment for premature infants who are at risk of developing RDS. Those less than 32 weeks gestational age and/or of birth weights less than 1.25 kg. Early administration may help to minimize lung injury, which could otherwise be the result of ventilating surfactant-deficient lungs. The instillation of exogenous surfactant into lungs that are still absorbing fetal lung fluid may result in improved distribution.[3]

Instillation of surfactant

The most common method used for administering exogenous surfactant is direct instillation into the endotracheal tube. This method results in a rapid spread of material, allowing it to be distributed to the lung periphery. Other methods of investigated administrations include aerosolization of the surfactant as well as instillation in combination with techniques such as jet ventilation and partial liquid ventilation.[3]

General information on the dosage for various surfactant replacement products is shown on **Table 1.**

Clinical Trials

Investigations of various exogenous lung surfactant preparations that are presently available have demonstrated differences in the improvement of gas exchange and other pulmonary variables. However, they have failed to show a statistically significant reduction in mortality or increased survival without bronchopulmonary dysplasia (BPD).[3] There does appear to be some indication that the presently available natural surfactants may be more efficacious than synthetic preparations when administered to premature infants. It is also important to note that differences do exist among the natural surfactants; therefore the individual characteristics of each must be considered.[3]

TABLE 1. DOSAGE RECOMMENDATIONS FOR COMMONLY USED EXOGENOUS SURFACTANTS[3]

Product	Dosage	Additional Doses
Calfactant	3 mL/kg of birth weight given in two aliquots	May be repeated every 12 hours for up to three subsequent doses at 12-hour intervals, if indicated
Beractant	4 mL/kg of birth weight given in quarter doses	May be repeated after at least 6 hours, up to a total of four doses within 48 hours of birth
Colfosceril	5 mL/kg of birth weight given over a 4-minute period	May be repeated after 12 hours and 24 hours, if indicated
Porcine	2.5 mL/kg of birth weight given in two aliquots	Two subsequent 1.25-mL/kg doses given at 12-hour intervals, if indicated

Adverse effects of surfactant

One of the undesirable effects that may arise due to surfactant therapy is transient airway obstruction (correlated with transient hypoxemia and hypotension). Changes in cerebral perfusion may also occur in very premature babies owing to the rapid redistribution of pulmonary blood flow into cerebral circulation. Rales and moist sounds may occur transiently, however these are normal findings. Other effects are transient bradycardia (11.9%) during multiple dose trials, oxygen desaturation (9.3%), reflux, pallor, vasoconstriction, hypotension, hypertension, tube blockage, hypo/hypercarbia, and apnea.

All effects may be resolved simply by stopping the treatment or increasing oxygenation and ventilation.[4,11]

Procedural and physiologic concerns

Points to be considered when employing surfactant therapy:[3,10]

1. Endotracheal tube occlusion, bradycardia secondary to hypoxia, and hemoglobin desaturation due to the procedures, is suggested to give sedatives.
2. Close monitoring by qualified personnel is necessary in order to minimize the impact of complications.
3. Physiologic complications include apnea, the development of mucous plug, and pulmonary hemorrhage. Frequently, an immediate improvement in lung compliance occurs, resulting in an increase of expiratory tidal volume. Observation of increased chest expansion should be done. Failure to make ventilator adjustments in response to improved lung compliance has results in barotrauma, as well as volutrauma.
4. Sepsis is the most common complication in ventilated babies, incidence as high as 67% has been reported.
5. The increased incidence of PDA in babies who did not receive surfactant could be explained based on the known association of PDA and septicemia in the premature neonates.

Implications for practice

Some studies indicate that infants with RDS treated with early surfactant replacement therapy and nasal continuous positive airway pressure (NCPAP) are less likely to require mechanical ventilation than those treated with NCPAP and later surfactant therapy. Current evidence is insufficient to rely on evaluating the effect of BPD or chronic lung disease (CLD). The amount of evidence should increase markedly when several concluded trials of such therapy are reported.[12]

Surfactant therapy in developing countries

Although it is still expensive, the use and availability of surfactant has increased globally, including Indonesia. In fact, there is still dilemma since several countries still face primary health care problems; on the other hand, there is a demand and need from certain levels or segments of the population which require surfactant treatment. Some factors should be considered in terms of surfactant use in developing countries.

The cost of surfactant is still high and variable ($800-1000/vial), which is high for developed countries. This may indeed be twice per capita income in some countries (Indian per capita $350/year). Thus it is the least cost effective. The aspect has been well studied in some countries where a development of policy for selective and restrictive use has been proposed. Similarly, other developing countries should develop such strategies. Alternately pharmaceutical industries should make efforts to produce low cost surfactant. In Indonesia, the price is around Rp 4,000,000,- (four million rupiahs), it is equivalent to US$37-40 per vial and no local product is available.[6]

Surfactant use presupposes the availability of trained personnel to manage neonatal ventilation and facilities to provide total intensive care. This in itself is a major undertaking. To establish a denovo, a NICU bed may cost $50,000 in equipment alone. The space, utilization, availability of personnel (nursing, technicians), etc. will add up to the cost. In developed countries per diem cost of such operation exceeds $1500/NICU bed; obviously high tech care is highly expensive. One should be fully aware of such cost analysis prior to introducing NICU in hospitals. The best alternative is to develop preventive strategies (improved prenatal care, antenatal steroids) and development of a regionalized system to pool resources and develop policies for treatment.[6]

Besides the existing benefits from surfactant therapy, there are also increasing complications to be

considered, such as infections, lack of nutritional support, and intra-ventricular hemorrhage (IVH). These complications were attributed to lack of skilled personnel, or capabilities to minimize infections or improve nutritional support of extremely small weight infants who survived longer periods of time after surfactant therapy. These observations indicate that surfactant therapy alone without proper supporting measures will increase the burden of the disease and prove to be less cost effective.[6]

In view of some observations, one might consider treating infants with surfactant either by aerosol (which will still require intubation) or use of single intubation for surfactant instillation followed by NCPAP. Studies of aerosol treatment of surfactants are in progress but not yet available for clinical use. Single intubation for surfactant treatment followed by CPAP has been reported by a few investigators. There is a limited use specifically in larger infants. The need for superb nursing care of these infants must be clearly recognized.[6]

Recommendations of Canadian Pediatrics Society

The recommendations of Canadian Pediatrics Society (**Table 2**) may have come from a developed country; however, it is important to consider surfactant therapy as a general and universal recommendation, including in Indonesia. Further research into retreatment criteria and optimal timing of prophylactic therapy is required.

TABLE 3. GRADE OF RECOMMENDATION REGARDING THE LEVEL OF EVIDENCE ACCORDING TO THE CANADIAN PEDIATRICS SOCIETY

Recommendation	Grade
Mothers at risk of delivering babies with less than 34 weeks gestation should be given antenatal steroids	A
Mothers with threatened delivery before 32 weeks gestation should be transferred to a tertiary centre if at all possible	B
Exogenous Surfactant therapy should be given to:	
• Intubated infants with RDS	A
• Intubated infants with meconium aspiration syndrome requiring more than 50% oxygen	A
• Sick newborn infants with pneumonia and an oxygenation index greater than 15	C
• Intubated newborn infants with pulmonary hemorrhage which leads to clinical deterioration	C
• Intubated infants with RDS before transport	C
• Infants who deliver at less than 29 weeks gestation outside of a tertiary centre should be considered for immediate intubation followed by surfactant administration after stabilization, if competent personnel are available	A
Natural surfactants should be used in:	
• Preference to any artificial surfactants available at the time of publication of this statement	A
• Infants who are at a significant risk for RDS should receive as soon as they are stable within a few minutes after intubation	A
Repeated dose or re-treatment should be given to:	
• Infants with RDS who have persistent or recurrent oxygen and ventilatory requirements within the first 72 hours. Administering more than three doses has not been shown to have any benefit	A
• Infant with persistent or recurrent oxygen requirement of 30% more and may be given as early as 2 hours after the initial dose or, more commonly, 4 to 6 hours after the initial dose	A
Options for ventilator management that are to be considered after prophylactic surfactant therapy include very rapid weaning and extubation to CPAP within 1 hour	B
Centers administering surfactant to newborn infants must ensure the continuous on-site availability of competent and licensed personnel to deal with acute complications of assisted ventilation and surfactant therapy	D

Grade A = Consistent level 1 studies
Grade B = Consistent level 2 or 3 studies
Grade C = Level 4 studies
Grade D = Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Conclusions

Since level 3 neonatal services or NICU are being developed in several centers or hospitals around the country, therefore the knowledge and expertise regarding surfactant should also be trained to qualified personnel. Data concerning the use of surfactant among hospitals in Indonesia varies from never, very rare, rare and often such data could not yet be represented.

References

1. Jobe AH. Pulmonary surfactant therapy. N Engl J Med 1993;328:861-8.
2. Interactive Respiratory Physiology Dictionary. Johns Hopkins School of Medicine. Surfactant. Available from: URL: http://oac.med.jhmi.edu/res_phys/Dictionary.HTML
3. Nuccio P, Pantano C. Surfactant replacement therapy. RT [serial online] 2001 June-July. Available from: URL: http://www.rtmagazine.com/issues.ASP?issueid=0106
4. Marraro GA. Exogenous surfactant supplementation. Available from URL: http://www.picu.it/india/surf_syllabus_marraro.pdf
5. Canadian Pediatrics Society CPS Statement: FN 2005-01. Recommendations for neonatal surfactant therapy. Available from: URL: http://www.cps.ca/english/statements/FN/fn05-01.htm
6. Vidyasagar D. Surfactant in ELBW infant. In: Rao MN, Vidyasagar D, Fernandez A, editors. Recent advantages in neonatology. New Delhi: Jaypee Brothers; 2004. p. 91-103.
7. Chernick V. The treatment of hyaline membrane disease. In: Smith GF, Vidyasagar D, editors. Historical review and recent advances in neonatal and perinatal medicine. Mead Johnson Nutritional Division; 1980. Not Copyrighted By Publisher. Available from: URL: http://www.neonatology.org/classics/mj1980/ch16.html
8. Vidyasagar D. Surfactants. In: Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. New York: Futura Publishing; 2000. p. 400-13.
9. Horbar JD, Carpenter JH, Buzas J, Sol RF, Suresh G, Bracken MB, *et al*. Collaborative quality improvement to promote evidence based surfactant for preterm infants: A cluster randomized trial. BMJ 2004;329:1004.
10. Narang A, Kumar P, Dutta S, Kumar P. Surfactant therapy for hyaline membrane disease: The Chandigarh experience. Indian Pediatr 2001;38:640-6.
11. Vidyasagar D. Review of surfactant therapy in neonatal respiratory distress. In: Rao MN, Vidyasagar D, Fernandez A, editors. Recent advantages in neonatology. New Delhi: Jaypee Brothers; 2004. p. 78 -90
12. Stevens TP, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev 2004 (3):CD003063.