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Newer Insight In Surfactant Delivery Methods: A Review Article

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ABSTRACT

Preterm lung is fragile and deficient of surfactant, which is why most preterms suffer from respiratory distress syndrome. Administration of antenatal steroids and use of exogenous surfactant has played a very important role in decreasing the incidence of mortality and morbidity in preterm infants. The commonest route of administration of exogenous surfactant is through the endotrechial tube post intubation. But, due to increased popularity of non invasive ventilation in both term and preterm infants, various other methods of surfactant administration has come into light. Through this review we will try to throw some light on different ways through which surfactant administration can be done in preterm neonates.

Keywords: Surfactant administration, preterm, non invasive ventilation, review, respiratory distress syndrome.

Exogenous surfactant therapy has been the main component of treatment for premature neonates with respiratory distress syndrome, for decades. Surfactant is a complex compound which is produced by type ll alveolar epithelial cells of the lung. It contains a comples mixture of proteins , lipids and carbohydrates which helps in decreasing the surface tension of the alveolar interface. Surfactant is either administered by placing an endotrechial tube, followed by mechanical ventilation or via brief intubation InSurE (INtubate, SURfactant, Extubate) technique.

With the increased survival of extreme low gestational age neonates (ELGAN)< 28 week´s non-intubated, **non-invasive ventilation (NIV)** has gained increased popularity in the neonatal intensive care unit (NICU) which has led to newer approaches of surfactant administration.

Recommendations for neonatal surfactant therapy (Canadian paediatric society)

- Infants with RDS who are intubated should receive exogenous surfactant therapy (grade A)
- Prophylactic natural surfactant therapy should be started in infants who are in risk of RDS,soon after intubation and satbalization (grade A)

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- Readministration of surfactant can be considered if the infant's FiO2 requirement is recurrently or persistently more than 30%. Commonly its done within 4 to 6 hours post first administration but within 2 hours is also accaptable (grade A)
- Immediate intubation followed by surfactant administration after stabilization,to infants delivered at less than 29 weeks gestation outside of a tertiary care centre, if competent personnel are available (grade A)

Also, recent recommendations state that premature newborn babies who has not received any resuscitation should receive non-invasive forms of respiratory support as far as possible.(1) But neonates having signs and symptoms of respiratory distress syndrome (RDS), for whom surfactant is of potential benefit, (2-4) administration of surfactant on non-invasive ventilation (NIV) is still a dilemma. Exposure to a few large volume breaths through PPV for a short duration also, can be enough to create lung injury. Keeping this in mind various techniques of surfactant administration are being developed to avoid intubation and need for positive pressure ventilation are being developed. The purpose of our paper will be to review these techniques along with their associated clinical evidence..

As mentioned above, intubation can lead to hazardous outcomes. Even premedication before intubation can have harmful effects to the baby causing prolonged intubation due to respiratory depression. To address the above mentioned problems,"minimally invasive surfactant therapy" (MIST), technique has been adopted where intubation with endotracheal tube is not required for surfactant delivery. These methods are as follows:

(1) Intraamniotic route,

(2) Pharyngeal route,

(3) Through laryngeal mask airway,

(4) Through thin endotracheal catheter without IPPV,

(5) Via aerosolization/nebulization of surfactant in a spontaneously breathing neonate.

Intra-Amniotic Instillation of Surfactant

This technique involves delivery of surfactant via endoscope directly to the fetus.This is done at the time of preterm labor. Petrikovsky et al. (5) used a gas-sterilized fiberscope to administer surfactant into the amniotic cavity via cervical canal after spontaneous rupture of membranes. This was done after the membranes had ruptured spontaneously. In another study with the help of this approach surfactant was administered into the mouths of three preterm infants via fiberscope. Even though complications with this study were not reported, still there is need for further prospective studies, just to have more knowledge regarding the safety and effaicacy of this method. So far, this technique is not being incorporated in any clinical practice.

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Pharyngeal Instillation of Surfactant

It is one of the oldest method of surfactant administration where the surfactant is deposited into the pharynx with the help of syringe which is attached to a short tube. This process is done before the baby takes the first breath**.** Some of the surfactant is inhaled while the rest of it is swallowed.

Term babies create a significant positive transpulmonary pressure by inspiration followed by closing the glottis during expiration. This process helps in forcing the lung fluid of the fetus into the interstitium (6). It in turn establishes an air-fluid alveolar interface with deposition of the surfactant from the fluid present in the lung. However, in a premature baby, there is deficiency of surfactant, therefore a similar phenomina may cause lung injury where alveolar integrity is disrupted (7), cytokines are released (8), protein leak occurs (9), and both endogenous and exogenous surfactant are in activated (10).When surfactant is administered pre delivery through pharyngeal route, , normal physiological process of chest expansion and alveolar recruitment,can be replicated. In this method surfactant is administered by replacing the upper airway fluid with an exogenous surfactant solution, which is then aspirated by the baby as the chest expands, providing surfactant at the air-fluid interface. To aid the whole process, application of CPAP may be required post instillation.

Enhöerning and Robertson, in 1972 used a premature rabbit model to evaluate this method and found it to be beneficial in improving lung function. (11)

In 2004 the report on pharyngeal instillation of surfactant was initially published (12),in which twenty-three infants (27 and 30 weeks' gestation) were taken for the studyand were administered with surfactant (Infasurf) within the nasopharynx. The surfactant administration was done before the delivery of the shoulders,followed by CPAP for at least 48 hours. The technique was reported to be relatively simple and safe, but was limited to only spontaneously breathing infants born through vaginal deliveries. In malpresentation (breech or transverse), cesarean section or perinatal compromise this method cannot be utilized. On cochrane review no such articles were found which compared this approach to no treatment or treatment with endotracheal intubation and surfactant administration (13). Recently, in a study premature infants (born <25 weeks) , showed to have a reduced need for intubation in the delivery room after they were given oropharyngeal surfactant(14) However, another European multicentre RCT (EudraCT 2016-004198-41) has shown no benefit of delivery room pharvngeal surfactant administration in preterms (<29 weeks' gestation), also there was no difference in the rate of prolonged intubation or incidence of death and BPD.(15)

Although this process is less invasive process, a significant limitation is that we cannot measure the proportion of surfactant that actually goes into the lungs (16).

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Administering via Laryngeal Mask Airway (LMA)

Laryngeal mask airway (LMA) is a device which is used for ventilation by pacing it over the supraglottic structures. The mask is elliptical in shape and is attached to a large endotracheal tube.The advantage of the mask is that , it can be inserted blindly into the infant's posterior phrynx. A tight seal is then created around the upper esophagus by inflating. Because LMA can be placed in the posterior pharynx without the need for visualization of the vocal cords This method is used in establishing effective ventilation without the requirement of intubation, and can be performed by health workers who are not very experienced. Various types of LMAs are: Classic; Pro Seal; I -Gel; PAX press; Cobra PLA .

The use of LMA for surfactant administration was done in 2004 by Brimacombe et al. for the first time.(17) and by Trevisanuto et al., a year later(18) in preterm infants.

Trevisanuto(19) suggested using LMA for surfactant administration which involved positioning of the LMA, followed by surfactant administration,in aliquots, through it. It is generally followed by intermittent positive – pressure ventilation for a short time until the disappearance of surfactant from the LMA. The baby is put on CPAP for subsequent management after removing the LMA.

No studies yet reported for prophylactic or early surfactant administration through LMA(20).Though there was a small comparative study of late rescue LMA administration of with or without surfactant where, in the LMA group it was seen that there was a reduction in the mean FiO_2 requirement for maintaining a target saturation for 12 hours after the intervention. No other significant differences were reported (21).

There can be some possible adverse effects surfactant administration by LMA, such as hypoxia and bradycardia during surfactant delivery, laryngospasm, and even malposition of the LMA(22).As smaller LMA sizes are not easily available for use in extremely premature infants, it accounts for a major limitation(22). More well-designed studies are required to confer the safety and efficacy in this area.As surfactant is only approved for delivery through an endotracheal tube and Food and Drug Administration (FDA) has not approved for any kind of drug delivery through LMA, therefore its use is very much limited.

Administration via Thin Endotracheal Catheter/Feeding Tube without IPPV

A, thin intravascular catheter or feeding tube, using Magill forceps, is inserted below the vocal cords, under direct laryngoscopy. This technique is called "MIST" technique. This process is usually done during nasal CPAP therapy. While the infant is on CPAP the catheter is placed and the surfactant is administered slowly over a period of 3 mins. A detailed analytical study was done including premature infants ≤27 weeks of gestation. In this observational study, it was seen that there was reduced mortality and reduced rate of severe IVH when compared with historical control[19]. After the study this method was adopted by

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some centers in Germany and a retrospective analysis of data, from 15 centers, was conducted. It was observed that preterm infants who were treated with the new method showed less death or BPD, also there was lesser need for any respiratory support. There have been some technical difficulties associated such as using a highly flexible feeding tube or the need of Magill forceps to advance the thin tube into the trachea, which can become a limitation for this method.

Dargaville et al. conducted a study to overcome the above limitations imposed by the flexible feeding tube by using a 16-gauge vascular catheter instead. He placed without using Magill forceps or any premedication, below the vocal cord of the infant.25 preterm infants were enrolled in this study requiring any CPAP pressure or FiO_2. In all cases, surfactant was successfully administered followed by CPAP. Favorable outcomes were reported and there was decreased in the rate of intubation in the initial 72 h in the preterm (25–28-week) infants compared to control group (24).

Need for laryngoscopy and the use of Magill forceps are the limitations of this method. There are chances of causing trauma especially in active preterm infants,particularly, while placing the catheter without sedation. A Benevista gas jet valve to provide CPAP was used during pharyngeal administration of surfactant. There was proper dispersion of surfactant particles with this high flow CPAP device. The effectiveness of this method with Bubble CPAP is yet to be made clear.

Aerosolized/Nebulized Surfactant Administration in Spontaneously Breathing Infants

It is being assumed that the administration of an aerosolized or nebulized surfactant can be the best non invasive methods of all possible strategies to administer surfactant early in preterms with RDS, requiring minimal skill (23). The success of aerosol delivery dependant on various factors. These include the severity of respiratory distress syndrome, the surfactant type which is being used, aerosolization or nebulization method, the lung recruitment strategy employed and the age of infant,.For a surfactant delivery to be effective, four steps need to be accomplished. First, the need for aerosolization of the surfactant. This process may end up denaturing the surfactant proteins. Second, appropriate particle size so that it does not “rain out” in the airway and penetrate deep into the lung. Third,there should be reaggregation of the particles at their site of action. Finally, the reaggregated surfactant particle should maintain their biological activity.

Nebulized surfactant use definitely seem to be the most sophisticated and minimally invasive technique. A lot of pilot studies have used this method of delivery (24–29). In most of the studies nasal CPAP was used for delivery. One of the studies showed an improvement in Silverman score,(A-a) O_2-gradient and $PaCO_2$ (24) but another study failed to demonstrate its efficacy (25). But it is very difficult to compare, as the surfactant preparations were different and different devices were used for nebulization and deliveries, these included jet

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nebulizers, vibrating membrane nebulizers and ultrasonic nebulizers. Also, the ages at the time of application also varied between minutes to days.

Arzhavitina compared six different types of nebulizers and hypothesized that the best among all the devices for surfactant delivery was the vibrating membrane nebulizer, because it had maximum output and minimum residual volume in the device. (30).

In the year 1964 Robillard et al.(31) administered a synthetic preparation (L-α-lecithin) directly into the incubator by aerosolization assuming that the infants will inhale the surfactant. Eleven neonates were included in this study with birth weight between 680 – 3120gms. Out of the eleven improvement was seen in Eight neonates and they survived to discharge.

The largest study till now, using aerosolized surfactant, was reported by Cummings et al. in the year 2020(32) This study was a randomized phase 3 trial and multiple centers across the United States were included. In this study two group of infants were compared, one group had received surfactant through the usual method and the other group through aerosolized method. The study group had received aerosolized calfactant. The results showed that in aerosolized calfactant group only 26% of the infants required endotracheal intubation and liquid surfactant administration while in the usual care group 50% required so.

Till now there has been very limited progress in this area as there are only 6 published studies, out of which only 2 were prospective RCTs(33,34)

As of now,there no commercially available device which can deliver aerosolized surfactant. The modified Solarys device is currently under review by the U.S. FDA. There are other similar devices also from different manufacturers which are undergoing clinical trials. Eventually more such devices will be available in the market.

CONCLUSION

With this review we come to a conclusion that there has been a lot of progress in the field of intensive care of new born babies which also involves preterm and extremely preterm neonates lo a greater extent and aim is to achieve an intact survival. For this non invasive methods of ventilation and even surfactant delivery is being adoped in various NICUs. A lot of researches has been done and a lot yet to be done. All methods in this review has a lot of potential for future use of delivering surfactant and can be highly beneficial in rendering intact survival of the neonate.

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