Non-invasive surfactant administration in newborn babies

The use of the laryngeal mask airway (LMA) for the administration of surfactant in respiratory distress syndrome in newborn babies is discussed as a tool to reduce invasive intubation. The author's personal experience and observations following surfactant administration by LMA are described.

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Key points

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1. The laryngeal mask (LMA) is a non-invasive extraglottic device.
2. It is easy to use and enables intubation to be avoided in many preterm and term infants.
3. The LMA has been used to safely and effectively administer surfactant in spontaneously breathing infants with moderate respiratory distress syndrome.
4. Further developments of the LMA will improve its effectiveness.

The present trend in neonatal medicine is to reduce invasiveness; with the aim of lessening unnecessary procedures which themselves may result in a worsened outcome and it is clear that some preterm infants do not need intubation. However the benefit of surfactant to reduce the severity of surfactant deficient lung disease is without question. Until recently the primary intervention in many premature infants was early intubation followed by ventilation, often with supplementary oxygen concentration of 100% and the administration of pulmonary surfactant (SF) via the endotracheal tube. One of the main consequences of these actions in premature babies was that once intubated and ventilated it can be difficult to wean the baby from ventilation and the baby may remain intubated and ventilated, sometimes for days, increasing the chance of the development of bronchopulmonary dysplasia (BPD).

In recent years many new facts have come to light:

- Intubation and ventilation can be dangerous and traumatic procedures[1]
- Development of BPD – a chronic lung disease associated with prematurity – is directly related to the baro-and volu-trauma of mechanical ventilation and to the time the baby is maintained on mechanical ventilatory support.
- Intubation can result in occasional trauma to the vocal cords and subglottis provoked by the endotracheal tube[2-4].

Recognition of these facts has led neonatologists to modify their approach to the respiratory support of the preterm baby, although when considered necessary exogenous SF is still administered to the lungs of babies with respiratory distress syndrome (RDS) via an endotracheal tube, after intubation.

In the dynamic process of reducing invasiveness in preterm infants with RDS, a method of administering exogenous SF into the lungs using temporary intubation followed by extubation to nasal continuous positive airway pressure (nCPAP) after a brief period of manual or mechanical ventilation was developed – INSURE (INtubation, SURfactant administration, Extubation)[5]. This avoided prolonged mechanical ventilation and even short-term mechanical ventilation was not necessary in a significant number of patients[6]. However the INSURE method cannot avoid intubation altogether, even for just a short period, and it is therefore still an invasive manoeuvre.

Following reports of the successful delivery of SF with a non-invasive extraglottic device called a laryngeal mask[7], this procedure was introduced at the author's centre to deliver SF to the trachea of infants suffering moderate RDS, with gestational age ≥32 weeks or birthweight ≥1500g.

The laryngeal mask

The laryngeal mask (LMA®) is a non-invasive, extraglottic device for airway management invented and developed by Dr Archie Brain at the London Hospital Whitechapel in 1981[8]. It consists of a rubber lozenge or mask lined with an inflatable cuff connected to a tube (**FIGURE 1**). When inserted the LMA sits at the junction between the oesophagus and the pharynx. The anterior pointed part of the mask enters the oesophagus while the remaining part occupies the pharynx and inflation of the cuff creates a closed cavity. The tube connected to the mask ends outside the mouth with a connecting piece for the balloon or the mechanical ventilator's tubing.

When the LMA is well positioned the outlet in the middle of the mask is sited

FIGURE 1 The classic laryngeal mask (LMA) in its various sizes. Within the circle the size # 1 that fits neonates 1500-5000g.

just in front of the larynx, and the oesophagus is sealed by the anterior part of the mask. A closed cavity is therefore created within the mouth by the lateral borders of the mask, the oro-pharynx and the posterior part of the tongue. In such a way air pumped into the tube from outside can easily reach the trachea without endotracheal intubation and at the same time exhalation is allowed. Spontaneous breathing and closure of vocal cords is not inhibited.

The LMA has so far been largely used in both paediatric and adult anaesthesiology. It has been estimated that over 150 million people have been treated with the LMA, and more than 60% of anaesthetic interventions have been conducted with the LMA in some UK hospitals, with greater than 99% success at the first attempt[9]. It has also been used for resuscitation, both in adults and babies[10,11], especially when conventional endotracheal intubation can be difficult, as in oral malformations, or dangerous, as in the case of facial trauma, with good results when it was utilised by paramedics or young doctors. Indeed the International Liaison Committee on Resuscitation (ILCOR), the American Academy of Pediatrics (AAP), the American Heart Association (AHA), and the European Resuscitation Council (ERC) have included the use of the LMA in their guidelines for neonatal resuscitation, with the provision that it must be used by skilled personnel[12-15].

New devices such as the Pro-seal LMA which is a development of the classic LMA enabling gastro-oesophageal suctioning, or other devices such as the laryngeal tube, have been promoted on the market, but data presented here are limited to that obtained with the classic LMA

which is what is used currently in the author's department.

Pulmonary surfactant

Surfactant is a lipoprotein mainly composed of dipalmitoylphosphatidylcoline (DPPC) and at least four associated proteins (apo-A, apo-B, apo-C, apo-D) that are present in minimal quantities but are extremely important to the action of SF. The main and most important function of SF is its ability to reduce the surface tension acting on the epithelium of the pulmonary alveolus. The surface tension is the pressure which has to be overcome to open the alveolus when its dimension is reduced at the end of an exhalation. As the surface tension is inversely related to the radius of the alveolus, the smaller the radius and therefore the smaller the alveolus, the higher the surface tension will be. The maximum surface tension is present at birth, when the alveolus has to expand for the first time. SF acts by reducing the surface tension allowing the first breath to open the alveolus and then – by creating a sort of chemical rigid skeleton thanks to the properties of DPPC – stabilises it, avoiding collapse of the alveolus at the end of exhalation. Thus SF permits a certain amount of air (functional residual capacity) to remain within the alveolus at the end of exhalation, and subsequent breaths require a smaller driving pressure because the radius of the alveolus is greater than zero.

As SF is produced by type 2 pneumo-cytes in sufficient amounts only after the 34th week of gestation, babies born before this gestational age will have difficulties in initiating stable respiration and a greater probability of developing the disease which results from SF deficiency – RDS, characterised by the presence of hyaline membranes within the collapsed alveoli.

Term or near-term babies can also develop a deficiency of SF due to other causes such as:

■ inhalation of meconium, eliminated *in utero* due to intrauterine asphyxia and perinatal infection, that competes physically or chemically with SF

■ lung immaturity as a result of maternal diabetes not well controlled during pregnancy

■ all the conditions that can limit the secretion of SF, eg acidosis of asphyxia, delivery by caesarean section not preceded by labour, drugs given to or taken by the

mother during or close to the delivery.

All these factors can result in a deficiency of pulmonary SF that can evolve toward RDS of varying severity. In some cases lung immaturity is not the *primum movens* of the disease, but probably consumption of SF or a block to its secretion are more important factors in the evolution of the respiratory failure. Administration of SF both as prophylaxis in the delivery room and as early treatment of RDS has been shown to be effective in significantly reducing the incidence of air leaks and BPD, and reducing mortality, even in babies less than 30 weeks' gestation[16-18].

Natural SFs were more effective than synthetics SFs in rapidly improving oxygenation, but the final outcome was not significantly different[19].

Previous experience of non-invasive surfactant administration

Non-invasive administration of a synthetic SF devoid of proteins (artificial lung expanding compound or ALEC) was attempted by Morley and colleagues in the early 1980s[20]. ALEC was given by a kind of dry aerosol at birth and repeated by endotracheal instillation, when the infant was intubated. Control infants were given normal saline. The only significant effect of ALEC in this study was reduction in mortality compared to the controls.

Its positive effect on pulmonary compliance was shown in another study in comparison with control babies given normal saline, but the effect disappeared six hours after administration[21]. However in a study in premature babies comparing ALEC with poractant-α (Curosurf®), a natural SF extract containing SF associated proteins B and C, mortality in the ALEC group was significantly higher (31 vs 14 %, p<0.006,OR 0.37 [95% CI 0.18-0.76]) and so the study was interrupted before its end[22]. The use of ALEC was eventually abandoned.
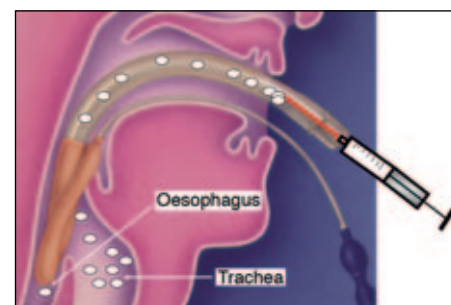

FIGURE 2 How surfactant is delivered by the laryngeal mask. The white ovals are particles of surfactant (Modified from Trevisanuto D[7])

In 2005 Trevisanuto et al published a paper[7] in which they showed that LMA administration of poractant-α at 200mg/kg, in eight babies with grade II-III RDS, was able to significantly increase the arterial/alveolar oxygen tension (a/APO$_2$) ratio (p<0.01) and significantly reduce the fraction of inspired oxygen (FiO$_2$)(p<0.01) three hours after SF administration (**FIGURE 2**). Babies had a range of bodyweights from 880g-2520g and gestational age from 28-35 weeks. All infants were on nCPAP before administration of SF at a mean age of 28 hours (range 2-68 hours) of life.

Initials	DG	MA	MG	SG	BD	ER	FN	PD
Gestational age, weeks	36	32	32	38	33	35	36	33
Body weight, g	2410	1490	1975	3850	2470	3120	2500	2185
Sex M/F	F	F	M	M	M	M	F	M
Delivery – caesarean (CS), vaginal (V)	CS	CS	CS	CS	CS	V	V	CS
Other pre-surfactant complicating diseases	Aortic stenosis	IUGR Twin	Twin	Hyper insulin-ism	PTX	----	PTX	----

TABLE 1 Main clinical details of patients given poractant-α by the laryngeal mask[22]. Key: IUGR-intrauterine growth retardation; PTX-pneumothorax.

FIGURE 3 Endotracheal administration of SF through the laryngeal mask.

FIGURE 4 Subsequent manual bag ventilation.

FIGURE 5 Removal of the laryngeal mask after its deflation at the end of the procedure. Note the baby was always on nasal CPAP.

Personal experience with LMA

Results of a study of eight babies by the author's group at La Spezia have been reported recently[23]. Babies ≥30 weeks' gestation, with moderate RDS diagnosed by clinical and radiological criteria and by oxygen requirements of 30-50%, were treated with poractant-α at 200 mg/kg. All babies were spontaneously breathing but required nCPAP support before admin-istration and had RDS diagnosed by chest X-ray, defined as moderate by the need for FiO$_2$ of 0.3-0.5.

After positioning the LMA (without removing nCPAP) and checking the position by brief manual bag ventilation with the same oxygen mixture as used for nCPAP, SF was injected as a bolus into the tube (**FIGURE 3**) of the mask, synchronously with a spontaneous breath of the baby, so that the SF was inhaled. Manual bag ventilation was then given to a maximum of 20cmH$_2$O pressure until the SF disappeared completely from the tube (**FIGURE 4**). Subsequently the LMA was removed and the baby at the same time re-started on nCPAP (**FIGURE 5**). Oxygen concentration was regulated by transcutaneous pulse oximetry (SpO$_2$) and reduced if SpO$_2$ exceeded 96%. At the end of the procedure a nasogastric tube was inserted into the stomach to detect if any SF was present. The babies ranged from 30-38 weeks' gestational age while body weights were 1490-3850g. Clinical details of the patients are reported in **TABLE 1**.

Mean FiO$_2$ was reduced from 0.53 before administration of SF to 0.33 within two hours of administration. During the same time frame, SpO$_2$ was maintained almost constant between 90-96%, but the mean PaO$_2$ doubled from 37.4 to 60.5mmHg and the mean PaO$_2$/FiO$_2$ ratio increased from 81.3% to 185.6% (Δ = +128%), showing an impressive improvement in oxygenation. In no case was SF found in the stomach. In the first three cases transient bradycardia and cyanosis occurred during the procedure possibly due to a vagal reflex. Consequently in subsequent cases atropine sulphate 20μg/kg IV was given immediately before the procedure. This was enough to avoid the reported problem. In no case was sedation necessary.

Although the effect on oxygenation by LMA SF was striking, it was not as immediate as after endotracheal administration. Examination of chest X-rays performed after administration, showed that the right lung appeared to have improved more rapidly than the left one. The theory is that this is because when SF is spontaneously inhaled by the baby, as with any other substance that is spontaneously inhaled in the supine or upright position, it naturally tends to be delivered mainly to the right lung, due to the angle of the right main bronchus. Thus the left lung improved only when SF was redistributed, and this process required a certain time interval.

In the standard method of bolus endotracheal SF administration, SF is pushed into the lungs with manual bag ventilation, using a pressure that can be greater than 20cmH$_2$O and moreover is positive – not negative, which may be more traumatic but does result in a uniform distribution. The highest pressure delivered by classic LMA is about 20cmH$_2$O, and above this pressure there is leakage from the lateral borders[24].

Statistical analysis was not indicated in this small group of babies, but the effectiveness of SF administration by this method was clearly evident. At La Spezia babies are continuing to receive LMA SF and at present a total of 13 newborn babies with a mean gestational age of 34.4 weeks and a mean body weight of 2420g has now been treated. In this group the PaO_2/FiO_2 ratio increased from the baseline value of 76.4% to 234.1% ($\Delta = +206$%) a further increase compared to the original eight cases. This improvement has been achieved by a change in the procedure: SF is administered in two divided aliquots, the first of which is given with the baby positioned on its left side and the second with the baby positioned on its right side. In such a way the distribution appears more uniform on chest X-ray.

Future developments of the LMA

The availability of smaller laryngeal masks in the future will make it possible to manage extremely premature babies and thus reduce some of the traumatic risks of mechanical ventilation deriving from endotracheal intubation.

Recent improvements make it possible to feed a baby while on mechanical ventilation using a LMA, even if at present the longest reported period of mechanical ventilation with LMA is about 44 hours[25]. Also, the use of the LMA as an introducer for endotracheal tubes without a laryngoscope and as a guide for a fibreoptic bronchoscope has been shown to be possible[26, 27].

Small LMA with visors, comparable to those in use for adults, might improve the positioning. Also SF administration via the LMA could be used in babies without RDS to administer drugs to the lung using SF as the vehicle.

Conclusion

More data and especially from a randomised controlled trial will be necessary to show the real benefits of the non-invasive procedure of SF administration by LMA in spontaneously breathing newborn babies who develop RDS. However it is clear that such a method of delivering SF is possible, easy to learn[28], effective, and can be performed in centres where there are no facilities for mechanical ventilation. This has the potential to improve the clinical condition of the baby while awaiting transport.

The hope is that in the future the management of babies becomes less invasive and more available at each hospital, without denying these vulnerable patients the potential for clinical improvement.

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