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MINI-SYMPOSIUM: NEONATAL LUNG DISEASE

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Approaches to the initial respiratory management of preterm neonates

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Summary Newly born preterm infants often require respiratory support. Various approaches have been taken to provide this support, including elective intubation and ventilation, prophylactic surfactant and continuous positive airway pressure (CPAP). Elective intubation and ventilation allow the clinician to take control of the baby's airway and reduce the support as tolerated. Surfactant can be administered prophylactically to prevent lung injury and respiratory complications. Many neonatologists, however, advocate a less aggressive approach to the provision of support, which includes the application of early nasal CPAP with intubation and ventilation only if necessary. Avoiding intubation may be effective in minimising ventilator-induced lung injury, but withholding surfactant may be detrimental to the infant. In this paper, we examine the advantages and disadvantages of the different approaches that can be taken in providing respiratory support to preterm neonates shortly after birth and examine some strategies that integrate them.

INTRODUCTION

The first few minutes after birth represent the most profound period of physiological adaptation that humans must undergo. The transition from intra-uterine life requires major changes to the respiratory and circulatory systems to allow a neonate to maintain adequate respiratory gas exchange without the benefits of the placental circulation. Remarkably, this complex series of events usually goes quite smoothly, and the role of the birth attendant is often relegated to that of an interested bystander. Some babies will, however, have difficulty with this transitional process and will require intervention and support to help them through it.

Inflation of the lung with air, the release of surfactant, the establishment of functional residual capacity, the reabsorption of lung liquid, increases in pulmonary blood flow and the establishment of a regular respiratory pattern are necessary for successful postnatal adaptation. Although any infant can have difficulty with these complex processes, those born preterm are particularly vulnerable to respiratory problems during this critical period. Within neonatal intensive care units (NICUs), these babies are often provided with various types of support to compensate for inadequate respiratory drive, abnormalities in their surfactant system and/or difficulties with the reabsorption of lung liquid. Assisted ventilation, continuous positive airway pressure (CPAP) and surfactant-replacement therapy are often used to support lung expansion and adequate gas exchange. These interventions have been very successful and the vastly improved survival rate for preterm infants over the past four decades can be directly attributed to their development and application. As smaller and smaller infants have survived with greater regularity, it has, however, become apparent that many of the survivors suffer from varying degrees of chronic lung disease (CLD).[1]

Clinicians have been disappointed by the results of trials evaluating interventions geared towards the reduction of lung injury and inflammation that investigators hoped would have a significant impact on the incidence of CLD. Indeed, modern NICUs continue to house a significant number of babies suffering from CLD. Refinements in

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the way in which respiratory support is applied to preterm infants may be able to affect the incidence of this troublesome condition.[2]

The preterm, surfactant-deficient lung is highly susceptible to tissue injury that then seems capable of triggering an exaggerated, unchecked inflammatory reaction.[3] Epithelial damage can be detected after only a few minutes of positive-pressure ventilation.[4] The respiratory management of preterm neonates during the immediate postnatal period may be key to minimising acute lung injury and its sequelae, including CLD. Support may be needed to assist a baby through the transitional process but it must be appreciated that there is a danger in applying interventions that are unnecessary or delivered in an overly aggressive fashion. This paper will review the various approaches that can be taken in the initial respiratory management of preterm neonates beyond resuscitation and their implications.

MECHANICAL VENTILATION

Respiratory distress syndrome (RDS) is characterised by pulmonary immaturity and surfactant deficiency, which lead to alveolar collapse, intrapulmonary shunting and poor lung compliance. The main goals when treating a baby with RDS are the maintenance of adequate oxygenation and minute ventilation. Although non-invasive techniques can be applied to facilitate gas exchange, mechanical ventilation is often used to establish and maintain an adequate lung volume and minute ventilation.

Historically, infants diagnosed with RDS were observed and initially treated with supplemental oxygen, usually in a head box.[5] If they deteriorated or could not manage with supplemental oxygen alone, they were intubated and placed on mechanical ventilation. It became clear that some babies could be rescued by the use of assisted ventilation, but the mortality rate remained high and many survivors were left with severe CLD.[6] As time passed and ventilatory techniques improved, some clinicians questioned whether it might not be more advantageous to intervene sooner with ventilatory support in order to secure the airway and prevent hypoxaemia and respiratory failure.

In 1982, Drew published a randomised controlled trial to test the hypothesis that the elective intubation of preterm neonates would produce better outcomes compared with standard management.[7] In that unit, standard management consisted of the provision of supplemental oxygen with selective intubation according to clinical criteria. A group of 165 infants weighing less than 1500 g at birth were randomly allocated to either immediate intubation and respiratory support or intubation only when necessary. Intubated babies were supported with either CPAP or assisted ventilation. The survival rate was significantly better for those infants who were electively intubated (77% vs. 51%). Histology of the lungs of the selectively intubated infants showed poor expansion and severe hyaline membrane disease. The electively intubated group had better physiological parameters for the first four hours of life, required lower ventilator settings and had fewer pneumothoraces. The results of this trial prompted many NICUs to adopt a practice of elective intubation for all infants born below a certain birthweight or gestational age that, in many cases, continues to this day.

There are several theoretical advantages to the practice of elective intubation and ventilation of preterm neonates that make this a popular approach (Table 1). Apart from the potential advantage to pulmonary function and performance, the most compelling reason for this approach is that babies are often easier to manage. A proactive approach in which the airway is secured and ventilatory support provided to babies who are very likely to need it eventually is very appealing. Without intubation, the management of a baby with evolving RDS can be very challenging, and it sometimes seems like one is waiting for the axe to fall.

There are, however, also several disadvantages to the practice of elective intubation and ventilation of preterm babies (Table 1). Not all small, preterm infants require assisted ventilation; therefore, it seems inadvisable to impose a very invasive therapy with its possible adverse consequences upon all of them. Laryngoscopy can cause profound changes in heart rate, oxygen saturation and blood pressure,[8] changes that may predispose to cerebral haemorrhage and neuronal injury. The passage of an endotracheal tube may cause trauma to the upper airway and assisted ventilation, especially if applied at an excessive setting, can cause lung injury[9] or cerebral ischaemia.[10] The acute ventilator-induced lung injury sustained shortly after birth can trigger the inflammatory cascade that leads to CLD.[3] It is difficult to know how many babies may have

Table 1 Advantages and disadvantages of elective intubation.

Benefits of elective intubation	Disadvantages of elective intubation
Helps to establish functional residual capacity	*Many infants can manage without an endotracheal tube*
Aids reabsorption of lung fluid	Adverse physiological effects of laryngoscopy
Promotes release of surfactant	May cause unnecessary trauma to the upper airway
Creates a "controlled" situation (neonatal intensive care unit, transport)	May cause unnecessary baro-/volutrauma
May prevent "collapse"	Inadvertent hyperventilation can occur
Allows prophylactic surfactant to be given	May increase cost

suffered significant iatrogenic complications simply because they were electively intubated and ventilated.

SURFACTANT-REPLACEMENT THERAPY

Avery and Mead established an association between RDS and a deficiency of surface-tension lowering substances in the lung in 1959.[11] From this observation, the concept of surfactant-replacement therapy evolved, this treatment now having become firmly established as one of the most important therapeutic advances in the field of neonatology. The treatment of preterm babies with RDS by the endotracheal instillation of exogenous surfactant has been shown to improve lung volume and compliance, decrease the need for supplemental oxygen and high ventilator settings, decrease air leak syndromes and lower mortality.[12]

It was clearly demonstrated in early case series that preterm babies with established RDS improved after treatment with surfactant.[13,14] Several investigators, however, strongly advocated a prophylactic approach as likely to be optimal. Enhorning and co-workers, who were the first to demonstrate the effectiveness of exogenous surfactant in a preterm animal model, suggested that surfactant should be instilled prior to the first breath at the air–liquid interface of the upper airways.[15] Randomised controlled trials evaluating surfactant-replacement therapy have shown that it is effective whether given shortly after birth to prevent RDS or administered selectively only to babies with established disease.[12] Either approach is considered acceptable but the superiority of one over the other remains a topic of active debate.

There is a considerable body of literature describing studies that reveal advantages of prophylactic surfactant. Deposition of surfactant at the air–liquid interface of the upper airways, as advocated by Enhorning *et al*., may aid in the reabsorption of lung liquid.[15] As mentioned above, epithelial injury in the lungs of a surfactant-deficient newborn can occur after only a few minutes of positive-pressure ventilation; the administration of surfactant prior to the initiation of ventilation is highly protective.[4] It also appears that exogenous surfactant is distributed more homogeneously when given at birth rather than after a period of assisted ventilation.[16]

Eight randomised clinical trials have been performed to examine the relative advantages and disadvantages of prophylactic compared with selective surfactant treatment. These have been reviewed and a meta-analysis performed by Soll and Morley for the Cochrane collaboration.[17] This analysis, which includes data from over 2800 preterm neonates, revealed that there was a lower incidence of pneumothorax and a lower mortality rate in infants given surfactant prophylaxis compared with those treated only after a diagnosis of significant RDS had been established. The data indicate that, when used in the highest-risk group (babies born at less than 30 weeks' gestation), prophylactic natural surfactant treatment will save one life for every 17 babies treated.

Despite this rather compelling evidence, many clinicians have been hesitant to embrace surfactant prophylaxis as the standard of care for babies in their care. There are sound reasons for this. Many babies, even those born at a very early gestational age, are surfactant sufficient and do not develop RDS. This is particularly evident when antenatal corticosteroid therapy is widely offered. The treatment of these babies with prophylactic surfactant results in unnecessary expense and exposure to a biological product from another species. Perhaps more importantly, elective endotracheal intubation is required to administer prophylactic surfactant reliably, and, as discussed above, this may predispose babies to serious iatrogenic complications.[18] Many clinicians believe that preterm babies are much more capable of managing without intubation and ventilation than has been previously believed and that, with close monitoring and less invasive forms of respiratory support, the morbidity rate can be reduced.[19,20]

EARLY NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE

In one of the first examples of "outcomes research" in neonatology, Avery *et al*. published a paper in 1987 that compared the respiratory outcome in 1625 infants born with a birthweight of between 700 and 1500 g from eight NICUs across North America.[21] The incidence of CLD, defined as need for oxygen at 28 days, was relatively consistent between seven units but the rate was much lower in the eighth. This centre, Columbia University Medical Center in New York City, appeared to have similar patient demographics and the survival rate was comparable but they quite clearly had better respiratory outcomes. Each of the eight centres was then asked to describe their practices regarding respiratory management. Again, Columbia stood out as being different from the rest. It was therefore reasonable to hypothesise that their low incidence of CLD resulted from their unique approach to the respiratory support of very low-birthweight neonates. The distinctive elements of their approach included:

- the provision of nasal CPAP shortly after birth to any infant showing signs of respiratory distress;
- the tolerance of a $PaCO_2$ as high as 60 mmHg before intubating;
- for those babies requiring intubation and ventilation:
  - (i) the avoidance of hyperventilation;
  - (ii) the prohibition of muscle relaxants;
  - (iii) the supervision of ventilatory management by one clinician.

Although it is not easy to tease out which aspects of the "Columbia approach" contributed most to the reduction in CLD, the avoidance of endotracheal intubation and mechanical ventilation is likely to be one of the most important elements, the early and liberal use of nasal CPAP being used to achieve this. Whereas CPAP was first introduced in the 1970s as a treatment for preterm babies with established RDS or to facilitate extubation,[22] the group at Columbia and their disciples advocate the elective application of nasal CPAP soon after birth. The rationale for this is that the CPAP will help to establish the functional residual capacity and promote the release of surfactant, thereby creating and maintaining an adequate air–liquid interface in the lung. They allow the $PaCO_2$ and FiO_2 to rise, tolerate apnoeic spells and reserve intubation for only those infants who demonstrate, without a doubt, that they require ventilation to survive.

The non-interventional approach advocated by those at the Columbia University Medical Center appeals to many clinicians and has been embraced in many NICUs. This approach remains, however, unproven, and some clinicians have been not only sceptical about its effect on CLD but also concerned about the possible adverse consequences of hypercapnia, an elevated oxygen concentration and recurrent apnoea. Neither the effectiveness nor the safety of the Columbia approach has been demonstrated by rigorous evaluation through the performance of large, randomised controlled trials. There have, however, been several cohort studies published that have examined the effect of introducing early elective nasal CPAP in various centres. Table 2 lists the studies, the populations described and the results.[23–27]

These studies describe the effect of a unit-wide introduction of early nasal CPAP as an alternative to elective or liberal intubation. Predictably, each study documents an increase in the number of babies who can manage without mechanical ventilation. Of greater significance, however, is the surprisingly large number of babies, even those born quite early, that can escape without ventilation. There does not appear to be an increase in the risk of complications and there is perhaps a suggestion of a decrease in the risk of death or CLD.

Although advocates of the Columbia approach claim to have very low rates of CLD in their units, success has not been universal. A cultural shift, considerable training and the commitment of a dedicated, well-staffed clinical team appear to be necessary for this approach to be viable.

THE CONUNDRUM

Those who advocate the Columbia approach emphasise that intubation should be reserved for only the most severely affected infants in order to minimise barotrauma/volutrauma, improve mucociliary clearance and reduce the incidence of CLD. This contrasts with the views of other practitioners who believe that the evidence in favour of elective intubation and prophylactic surfactant therapy is sufficiently compelling to make this the only acceptable standard of care for very preterm neonates.[17] The two approaches are mutually exclusive. If it is better for a surfactant-deficient neonate to receive surfactant-replacement therapy as soon after birth as possible, how can a clinician justify providing initial respiratory support with only nasal CPAP and supplemental oxygen? If the Columbia approach is to be used, when should surfactant be given in order to assure that an infant is not disadvantaged by a delay in treatment?

Several clinical trials have been designed to test methods of management that integrate the principles advocated by the Columbia group with expeditious surfactant therapy. Two studies by Verder and colleagues have looked at when surfactant should be given to babies initially managed with nasal CPAP. In the first of these studies,[28] 68 preterm infants (25–35 weeks) with RDS being treated with nasal CPAP were randomised to either continued treatment

Table 2 Studies examining the introduction of early nasal continuous positive airway pressure.

Authors (year)	Type of study	Birthweight (g)	Outcome
Jacobson *et al.* (1993)[23]	Before/after	<1500	Decreased need for MV (from 76% to 35%) Decreased ICH grade II–IV No difference in rate of death or CLD
Kamper *et al.* (1993)[24]	Descriptive cohort	<1500	25% needing MV 80% survival No CLD
Gitterman *et al.* (1997)[25]	Before/after	<1500	Decreased need for MV (from 53% to 30%) No difference in rate of death or CLD
Lindner *et al.* (1999)[26]	Before/after	<1000	Decreased need for MV (from 93% to 75%) Decreased rate of death or CLD (from 50% to 31%)
De Klerk and De Klerk (2001)[27]	Before/after	1000–1500	Decreased need for MV (from 65% to 14%) Decreased surfactant use Decreased rate of death or CLD (from 16% to 3%)

MV, mechanical ventilation; ICH, intracranial haemorrhage; CLD, chronic lung disease.

with CPAP or intubation and surfactant treatment followed by quick extubation. Of the 35 babies in the surfactant-treated group, 33 could be successfully extubated within 1 hour of treatment and were placed back on nasal CPAP. This single dose of surfactant, given when babies reached a FiO_2 of approximately 0.60, reduced the need for subsequent mechanical ventilation from 85% in the control group to 43%. Although there was no statistically significant difference between groups in terms of the complication rate, 15% of the control group died compared with only 6% of the surfactant group.

The positive results from this study prompted Verder and colleagues to design a second trial to evaluate whether earlier treatment with surfactant might further reduce the need for mechanical ventilation.[29] In this trial, published in 1999, 60 preterm infants (less than 30 weeks' gestation) with RDS being treated with nasal CPAP were randomised to receive surfactant when they required an FiO_2 of approximately 0.40 or to continue with CPAP until they required a FiO_2 of 0.60, as in the previous trial. In both groups, attempts were again made to extubate the baby shortly after the surfactant had been given. Earlier treatment resulted in a reduction in the need for mechanical ventilation from 68% to 25%. In the late-treated group, 26% died, compared with 9% in the early-treated group. It was of interest that the rate of CLD was very low in both groups.

The results of these trials are consistent with those of other randomised trials of surfactant therapy that have examined timing of treatment. It has been repeatedly demonstrated that surfactant-deficient preterm infants derive the greatest benefit from surfactant treatment when it is given early in the course of their disease.[17,30] It appears that preterm babies initially managed with nasal CPAP should be intubated and given surfactant if their oxygen requirement is increasing beyond an FiO_2 of 0.35–0.40. It is possible that outcomes could be improved further if they were treated with surfactant even earlier.

There is an appealing approach to the treatment of these babies that combines prophylactic surfactant and the liberal use of nasal CPAP that may be optimal in protecting infants from lung injury and other detrimental effects of mechanical ventilation. This approach involves intubating babies at significant risk of RDS shortly after birth, administering surfactant and then extubating them to nasal CPAP. A recent study performed in the UK has examined this method of management and compared it with several other commonly used approaches. The investigators hypothesised that the combination of prophylactic surfactant and early nasal CPAP would reduce the need for mechanical ventilation compared with other commonly used strategies for the respiratory management of preterm babies.

In the IFDAS trial, infants born between 27 and 29 weeks' gestation were randomised to be treated using one of four management strategies:

1. elective intubation, surfactant administration and extubation to nasal CPAP within 2 hours of age;
2. early nasal CPAP with selective intubation, surfactant administration and early extubation to CPAP (as per Verder et al.[29]);
3. elective intubation, surfactant administration and mechanical ventilation;
4. selective intubation, mechanical ventilation and surfactant administration based on clinical criteria.

The results of this trial have been presented and published in abstract form.[31] Randomisation occurred just prior to delivery, 237 babies being enrolled. Babies in both the early nasal CPAP groups were less likely to require mechanical ventilation. Prophylactic surfactant did not, however, appear to convey any additional advantage when early nasal CPAP was utilised. There were no differences between any of the groups in the incidence of CLD or other complications, but it should be noted that the sample size was relatively small and important differences might not have been revealed.

WHAT SHOULD WE BE DOING?

Any of the four approaches tested in the IFDAS trial must be considered to be acceptable for the initial respiratory management of preterm babies. For those born at the earliest gestational ages, however, the balance of evidence would suggest that prophylactic or early surfactant treatment should be given. In the hands of most clinicians, it will be deemed necessary for the vast majority of these babies to be intubated at some point so it makes good sense to intubate them early and administer surfactant when it is likely to be most effective. For preterm infants born at greater than 25 weeks' gestation, however, the picture becomes less clear. Early nasal CPAP as an alternative to early intubation and surfactant administration must be considered to be acceptable and may prove to be the most effective approach to take in most cases.

A more definitive answer may be forthcoming in the next few years with the completion of several large, multicentre, randomised trials that are adequately powered to determine whether one approach is better in reducing the risk of death or CLD. The COIN trial, which is being run in Melbourne, Australia, will study 600 infants of 25–28 weeks' gestation randomised to be treated with either elective nasal CPAP or mechanical ventilation (C. Morley, personal communication, 2001).

The Vermont Oxford Network is sponsoring a randomised controlled study that will compare the effects of three distinct methods of post-delivery stabilisation and subsequent respiratory care on CLD and survival in premature infants at high risk of RDS (R. Soll and M. Dunn, personal communication, 2002). In this trial, which is scheduled to begin in early 2003, 2106 babies of 26–29 weeks' gestation will be randomly allocated to one of three groups:

1. intubation, prophylactic surfactant administration and subsequent stabilisation on ventilatory support;
2. early nasal CPAP with selective intubation and surfactant administration for clinical indications;
3. intubation, prophylactic surfactant administration and rapid extubation to nasal CPAP.

A comprehensive programme of education and training will be an integral part of this trial. It is clear that participating centres must be comfortable with treating babies in each of the arms of the trial and well versed in the recommended strategies to be taken. This will be especially important for units that have not commonly used elective nasal CPAP for babies born at these early gestational ages.

CONCLUSION

The respiratory management of a preterm infant shortly after birth is critical for the baby to have the best opportunity for intact survival, but which is the most appropriate strategy to use is one of the most hotly debated issues in neonatology at present. Other current controversies exist, including the optimal CPAP delivery system and the initial mode of ventilation after intubation, but any discussion of these issues is beyond the scope of this article. The administration of prophylactic surfactant after elective intubation has proved to be successful in reducing mortality, but alternative approaches may be successful in further reducing mortality rates and/or influencing the incidence of CLD. The use of early nasal CPAP combined with an avoidance of mechanical ventilation has been advocated as a kinder, gentler approach to the management of these babies that can result in a reduction in the incidence of iatrogenic complications, including CLD. Although this may be the case, high-quality data to support this approach are currently scant. Large randomised trials that are underway should help clinicians to determine which tube to pull out in the delivery room.

PRACTICE POINTS

- The best supported approach to the initial respiratory management of very preterm infants includes elective endotracheal intubation and early administration of surfactant.
- An alternative approach which includes early application of nasal CPAP with selective surfactant administration may prove to confer greater protection to the preterm lung.
- Elective endotracheal intubation followed by prophylactic surfactant and early extubation to nasal CPAP may allow for the benefits of early surfactant while avoiding ventilator-induced lung injury.

RESEARCH DIRECTIONS

- Adequately powered randomized controlled trials that evaluate the effect of different approaches to the initial respiratory management of preterm neonates on important clinical outcomes are desperately needed.

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