Special Article

Changing Trends in the Management of Respiratory Distress Syndrome (RDS)

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Abstract. The management of respiratory distress syndrome (RDS) has advanced because of improvements in mechanical ventilators, promotion of antenatal steroids, availability of surfactant and overall advancements in neonatal intensive care. Intermittent mandatory ventilation still forms the mainstay of assisted ventilation. Newer modes of ventilation have not delivered the results as promised. Because of the continued high incidence of bronchopulmonary dysplasia, there is a renewed interest in non-invasive modes of ventilation like CPAP and nasal IPPV. The present trend is to follow gentle ventilatory strategies accepting higher arterial carbon dioxide and lower oxygen. The role of antenatal steroids has been established beyond doubt but still they fall short of universal acceptance. Surfactant replacement therapy is the standard of care for RDS but beyond the reach of majority in India. Postnatal steroids are out of vogue because of probable links with cerebral palsy and abnormal neurological outcomes. **[Indian J Pediatr 2004; 71 (1) : 49-54]** *E-mail: shivika98@hotmail.com*

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Respiratory distress syndrome (RDS) continues to account for significant mortality and morbidity in the neonatal intensive care unit (NICU). According to the year 2000 report of National Neonatal Perinatal Database (NNPD) involving 51,905 intramural deliveries , the incidence of RDS in our country was 1.9 % of all live births and it was the primary cause in 14.3 % of the deaths.[1] The incidence of RDS is inversely related to gestational age. In babies born at 28-32 weeks, RDS occurs in up to 50% of live births.[2] In the USA, 40,000 infants develop RDS each year. In India community based data for RDS is not available but by conservative estimates, the disease may be occurring in 2,00,000 babies annually.

The improvements in the management of RDS are closely related to the overall progress in neonatal intensive care. Starting from the classic studies of Avery and Mead in 1959 which established surfactant deficiency as the cause of RDS, we now have a much better understanding of the complex pathophysiology of RDS.[3] We shall discuss the advancements in the management of RDS under 4 headings : assisted ventilation, antenatal enhancement of lung maturation, surfactant therapy and lung protection strategies. In the end we shall review the changes that have occurred in our own country.

ASSISTED VENTILATION

Conventional positive pressure ventilation remains the mainstay of assisted ventilation in neonates with RDS and has substantially improved the outcomes. A better understanding of pulmonary pathophysiology has helped in designing optimum assisted ventilation strategies. In 1950s, infants with severe RDS had poor prognosis. They were treated with oxygen by mask and intravenous fluids. Initial attempts at artificial ventilation were done with negative pressure ventilators and subsequently with intermittent positive pressure ventilators. These feasibility trials brought out the difficulties of neonatal ventilation. Significant advances followed subsequently, which were useful in developing operator friendly and efficient positive pressure infant respirators. In 1960s, mechanical intermittent positive pressure ventilation became widely accepted as the standard treatment of RDS in newborn.[4]

Gregory *et al* were the first to report the use of Continuous Positive Airway Pressure (CPAP) in the treatment of RDS of newborn in 1971.[5] This was accepted as the missing link between oxygen and ventilatory therapy. This system had the possibility of keeping terminal airways open at end expiration, thereby avoiding atelectasis when surfactant was deficient and maximizing ventilation to perfusion ratios. This concept was hence , added to positive pressure ventilators and later was extended to provide continuous positive airway pressure through nasal prongs. In 1973, Agostino *et al* reported the first small series of infants with RDS treated with nasal CPAP.[6] This method takes the benefit of the fact that most neonates are nasal breathers and would spontaneously form a seal between the palate and the tongue. In case of too high pressure, the mouth could act as a natural pop-off valve. In preterm infants with RDS the application of

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CPAP is associated with reduced respiratory failure (requiring intubation and positive pressure ventilation) and reduced mortality.[7,8] In the recent years there is a resurgence of interest in the use of early CPAP as the primary mode of treatment of RDS.[9] This has been stirred by the reports of lowest rates of Chronic Lung Disease (CLD) from centers which use early CPAP the most.[10,11] Though initially this experience was confined to one center , it has been replicated by others.[12] Currently, there is a whole lot of research going on into improvements of design and mode of administration of CPAP.[13] Infant flow driver CPAP which can maintain more stable pressures throughout the respiratory cycle because of its design, can probably reduce the work of breathing and holds lot of promise.[14]

Nasal Intermittent Positive Pressure Ventilation (NIPPV) is another ' non-invasive' modality of ventilation which has recently come up . NIPPV augments CPAP by superimposing ventilator inflations on nasal CPAP. It has been shown to be more effective in preventing failure of extubation.[15] Current ventilators can synchronize the NIPPV breaths with infant's breaths.

Although assisted ventilation decreased RDS related mortality, earlier ventilators were associated with complications such as airleaks, Bronchopulmonary dysplasia (BPD) secondary to barotrauma and volutrauma, airway damage and intraventricular hemorrhage (IVH). Advances in microprocessor technology, transducers and real time monitoring have enabled patient- triggered ventilators and synchronization of mechanical ventilation with patient effort. Physiologic studies have demonstrated short-term benefits of patient triggered ventilation over conventional ventilation.[16] During synchronized mechanical ventilation, peak airway pressure and spontaneous inspiration coincide. Thus with synchronized ventilation adequate gas exchange can be achieved at lower peak airway pressures reducing barotrauma , air leaks and CLD. However these benefits have not yet been demonstrated in clinical trials.[17]

High frequency oscillatory ventilation (HFOV) , in which 600-900 breaths per second are applied at very small tidal volumes (less than the anatomical dead space) is another promising concept which has been tried over the last decade. Though very promising in terms of reducing barotrauma, the advantages have not been demonstrated in clinical trials. This may be due to lack of real understanding of the physiology of HFOV in initial years and application of sub-optimal strategies.[18]

Although positive pressure ventilation stays the backbone of neonatal ventilation, volume controlled ventilation is making a gradual comeback.[19] Current ventilators are able to control and deliver small tidal volumes suitable for neonates which was not possible earlier. The newest technology is able to combine the virtues of both pressure and volume controlled ventilation and deliver a 'guaranteed volume' within set pressure limits.[20] However, the clinical benefits of the newer modes of ventilation like volume guarantee and pressure support are yet to be demonstrated.

LUNG MATURATION THERAPIES

Antenatal Steroids

In the early 1970s, Liggins and Howie, while studying the effects of steroids on premature labor in lambs, noticed the lack of RDS and increased survival in preterm animals exposed to antenatal steroids.[21] Subsequently, multiple controlled trials have demonstrated their unequivocal benefit.[22] Antenatal steroids not only decrease the incidence and severity of RDS, but also overall neonatal mortality, intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC). Long-term follow-up of children exposed to one course of antenatal steroids have not shown any adverse effects.[23] The use of steroids however did not become widespread until after 1994 when the National Institutes of Health (NIH) published the consensus report.[24] Though a cheap and very effective intervention, its potential is grossly under-utilized even today. Initial reports comparing the effects of single course of antenatal steroids and placebo showed loss of apparent beneficial effects beyond seven days from the first dose of steroid. Therefore it became common practice to prescribe multiple courses of steroids on a weekly or rescue basis. However, there has been no data to document the benefit of repeated courses of antenatal steroids. Moreover concerns have risen regarding the effect of repeated courses of steroids on growth and long-term neurodevelopmental outcome.[25] Thus NIH consensus panel on repetitive courses of corticosteroids advocates that currently, there is not enough data to support the routine use of repeat or rescue courses of antenatal steroids.[26]

Thyrotropin Releasing Hormone (TRH)

The physiologic role of thyroid hormones in lung development and surfactant production has been demonstrated in lung cell culture, humans and other mammals. Prenatal administration of TRH appears to act synergistically with glucocorticoids in enhancing fetal lung maturation. In the initial clinical trials performed in the US and New Zealand, the combined use of prenatal steroids and TRH was associated with a significant reduction in the incidence of RDS and CLD.[27] However two large multicentric trials from US and Australia, failed to demonstrate any beneficial effects of combination therapy versus corticosteroids alone.[28,29] More important, long term follow-up from these trials showed worrisome neurodevelopmental outcome of patients in the TRH treated group.[30] Therefore the use of TRH for accelerating lung maturation cannot be recommended.

Surfactant Replacement Therapy

The discovery that surfactant deficiency was the key in

the pathophysiology of RDS led several investigators to administer artificial aerosolized phospholipids to infants with RDS. In these early trials only limited therapeutic success was encountered. In contrast, animal models in which natural surfactant compounds were used yielded more promising results. Fujiwara and coworkers in 1980 were the first to successfully administer a mixture of natural and synthetic surface-active lipids to 10 preterm infants with severe RDS who were not improving despite artificial ventilation. A single dose of surfactant instilled via the endotracheal tube resulted in a dramatic decrease in inspired oxygen needs, ventilatory pressures and better survival.[31] This was followed by a series of collaborative multicentric trials in which synthetic (Exosurf) and natural (Survanta) surfactant preparations were tested in thousands of infants.[32,33] Surfactant therapy has significantly decreased the mortality from RDS, overall mortality of ventilated preterm infants and even infant mortality rate in the West.[34] Currently, Surfactant Replacement Therapy is the standard of care for preterm babies with respiratory distress. In contrast to the improvements in mortality, the incidence of CLD has not changed much. The important role of surfactant associated proteins (SP-A,B,C, D) in the functioning of surfactant has been realized over the years and current efforts are to improve the composition of surfactant by incorporating these proteins.[35]

Other Therapies

Postnatal steroids: Although most of the studies using postnatal steroids have measured the incidence and severity of CLD as the primary outcome variable, some studies have looked at the acute effects of postnatal steroids in RDS. Two small studies in 1970s and 80s found no significant benefits with steroid administration in RDS . A small study from India showed benefits in terms of decreased oxygen needs and mean airway pressures.[36] However, the reports of increased cerebral palsy and neurodevelopmental handicaps in those babies who got steroids for CLD have dampened the enthusiasm for postnatal steroid use.[37] Till the results of currently ongoing prospective trials are available, postnatal steroids are generally avoided.

Supportive Therapy

Improvements in supportive perinatal care are one of the major factors for improved outcomes in babies with RDS. Their contribution cannot be segregated from the specific advances in the management of RDS. One of the major hindrances for success of neonatal ventilation during initial days was failure to take care of metabolic problems associated with prematurity, cold stress, starvation and circulatory problems . Along with the advances in ventilator technology , there have been important rapid advances in micro-techniques and online monitoring wherein multiple tests can be performed on small blood samples and physiologic information can be displayed continuously. They have played a very crucial role in improving the outcomes. Over the years, an improved understanding of neonatal physiology has contributed towards understanding the role of maintenance of oxygenation, perfusion, glucose homeostasis, thermoregulation, nutrition and specific organ supports. The role of minimal handling and analgesia has also been understood better in recent years.[38] The importance of developmentally supportive care to improve the neuropsychologic outcomes of these babies is being realized now.[39]

Current Focus: Lung Protection Strategies

With the advancements in mechanical ventilation, intensive monitoring and use of surfactant, the mortality due to RDS has declined to very low levels in the developed world. However, Chronic Lung Disease continues to be a big problem. With improving survivals of the most immature babies, the absolute burden of CLD has increased.[2] It is often impossible to determine how much of CLD is the sequel of RDS, its treatment or the underlying prematurity. Prevention of prematurity will be the utopia but currently is not achievable. There is a lot of effort and research on strategies to reduce the incidence and severity of CLD.

Northway and associates were the first to describe chronic lung damage in neonates subjected to assisted ventilation (1967) and introduced the term Broncho-pulmonary Dysplasia (BPD).[40] Ventilatory strategy and not necessarily HMD has been implicated as the prime factor responsible for the development of CLD. Measures to promote optimal lung inflation with sufficient alveolar recruitment (adequate PEEP) and avoiding alveolar over distension (decreasing PIP) are useful in decreasing ventilator induced lung injury (VILI).[41] Early use of nasal CPAP has been associated with decreased incidence of CLD.[10-12] The use of HFOV has not been conclusively shown to be effective in reducing CLD in infants, but data obtained in experimental animals suggest that HFOV may reduce lung injury.[18]

In the recent years, more and more neonatologists are accepting Permissive hypercapnia - a strategy that minimizes baro/volutrauma by 'tolerating' relatively high levels of $PaCO_2$ and lower levels of pH. The current concept that high $PaCO_2$ levels are safe and well tolerated is however, based on limited data. Further prospective trials are needed to the define the limits of safety and efficacy of hypercapnia in ventilated neonates.[42]

Because of the importance of inflammation in the pathogenesis of CLD, exogenous corticosteroids have been administered in a variety of regimens to reduce its progression. At one stage, it had become a common practice to administer dexamethasone if a baby continued to be on ventilator beyond 10-14 days of life. Then came a series of reports of increased cerebral palsy and neurodevelopmental handicaps in babies who had received postnatal dexamethasone.[43,44] This made people

very cautious about the use of postnatal steroids. American Academy of Pediatrics and Canadian Pediatric Society consensus committees concluded that systemic administration of dexamethasone to mechanically ventilated preterm infants decreases the incidence of CLD and extubation failure but does not decrease overall mortality. The treatment is also associated with an increased risk of short and long-term complications including impaired growth and neuro developmental delay. On this basis the routine use of systemic dexamethasone in VLBW is not recommended.[37]

It has been realized that having an endotracheal tube is the single most important risk factor for CLD. Hence, attempts are being made to avoid intubation by a variety of strategies. One of them is to apply early nasal CPAP and accept higher $PaCO_2$ (up to 60-70 mm Hg) and lower pH (up to 7.20) than have been the traditional cut-offs for intubation. Clinical trials have shown that intubate - give surfactant – extubate to CPAP approach can be effective in decreasing the need for mechanical ventilation and possibly minimizing CLD.[45]

RDS IN INDIAN SCENARIO

From the 1960s when it was believed that RDS is rare in India, we have come a long way. Today, nearly 30-40 centers across the country are ventilating neonates. Webb *et al* from Vellore were the first to report RDS in autopsy series as early as 1962. Still, most of the pediatricians did not believe it till a series of reports of RDS from various centers were published in early seventies. Mechanical ventilation was initiated in a few centers in late 1980s. In early 1990s, few academic institutions started ventilating neonates in a systematic and regular manner.[46,47] In the last few years, mechanical ventilation has spread rapidly and lot of private centers have also taken up ventilation in a big way. In a survey done by Bhakoo *et al* in 1995, 14 centers provided their data. It emerged that RDS was responsible for 36 % of the ventilations. The survival in RDS varied from 25 to 84 % between centers. The complications –sepsis , IVH and pneumothorax occurred in 29 %, 25% and 11% of ventilated babies respectively.[48]

Use of surfactant therapy was first reported in 1994 from Bangalore.[49] The first large experience of surfactant use in preterms with RDS showed significant improvements in survival and decrease in complications.[50] Initially, the drug was smuggled but now is licensed for import and sale, more widely available and the prices have decreased. It is still quite expensive; yet an estimated 150 - 200 doses of surfactant are being used every month across the country. With the entry of local manufacturers, the price is likely to reduce further substantially, making surfactant affordable for a large proportion of families. Till the use of surfactant became more widespread, diagnosis of CLD was rare in India. Like with RDS initially, it was believed that CLD is not our problem. This myth has again been disproven. The incidence of CLD in centers using surfactant is almost similar to that in the West.[51] With increasing use of surfactant and better survival of smallest of babies, we are likely to face an increasing burden of CLD.

More and more centers are investing in buying ventilators; what is of concern is that pari passu investment in intensive monitoring facilities as needed for ventilated babies is not taking place. As a result, we may be saving babies but their 'intact' survival is questionable. There are increasing reports of ROP already and virtually no information on long term neurologic and pulmonary outcomes of these babies.[52]

National Neonatology Forum (NNF) has taken some active measures to improve the situation. As early as 1992, an expert group meeting was held and recommendations for neonatal ventilation in the country were published.[53] An idea was mooted to set up a National Registry of Neonatal Ventilation which somehow lagged behind but would see the light of the day very soon. Responding to the demand and need, NNF , PGI - Chandigarh and AIIMS- New Delhi have been organizing training workshops in neonatal ventilation. There is an urgent need to update the 1992 NNF guidelines for neonatal ventilation and disseminate them widely.

CONCLUSION

Use of antenatal steroids , availability of mechanical ventilation and exogenous surfactant are the 3 main factors which have revolutionized the management of RDS. The burden of Chronic Lung Disease however has not decreased. Current and future strategies are likely to focus on use of non – invasive modalities of ventilation like nasal CPAP and acceptance of higher $PaCO_2$ and lower pH. In India, mechanical ventilation and surfactant use are spreading in a big way. However, a lot of caution needs to be exercised in their use and a careful audit of outcomes needs to be undertaken.

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