Ventilation, CPAP or surfactant for early management of respiratory distress syndrome – “continuing controversies”

ADEELA HOSENIE, SHALABH GARG, SUNIL SINHA

Abstract

Continuous positive airway pressure (CPAP) and surfactant are used in the therapy of respiratory distress syndrome. Effectiveness of these therapies is discussed in the paper.

Key words: respiratory distress syndrome, CPAP, surfactant

Preterm babies are at risk of respiratory distress syndrome (RDS) and require mechanical ventilation to keep them alive. However, there are complications associated with mechanical ventilation which are mostly iatrogenic. Of these, Ventilator-Induced Lung Injury (VILI) [2] has long been recognised as a contributor to the development of bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD). There has been increased interest in continuous positive airway pressure (CPAP) as a primary ‘gentler’ mode of respiratory support in RDS in a bid to improve mortality and reduce the occurrence of long-term respiratory morbidity.

Mechanical ventilation

Historically, oxygen was the mainstay of management of RDS in preterm neonates until positive pressure ventilation via placement of an endotracheal tube paved the way for improved respiratory support of these neonates in the 1960s. In 1967, Northway et al. [3] first reported BPD in a cohort of preterm infants who suffered from respiratory distress syndrome. These babies had received prolonged mechanical ventilation at high pressures and with high oxygen requirement. Northway et al described the clinical, radiological and pathological findings that characterised BPD. With the survival of preterm infants at lesser gestation over the last decades, this pattern of BPD has since changed giving rise to the ‘new’ BPD associated with less inflammation and abnormal postnatal lung development [4]. However, the incidence of BPD remains high with ventilator-induced lung injury (VILI) being a major factor. Ventilation also involves placement of an endotracheal tube which can have associated complications such as subglottic stenosis and respiratory infections.

CPAP

Management of RDS with continuous positive airway pressure was first described in 1971 by Gregory et al [5]. In their study, CPAP of up to 12 mm Hg was delivered to 20 infants via an endotracheal tube or head box later known as the ‘Gregory box’. The authors reported a survival of 70% in infants weighing less than 1 kg. However, they did not investigate the long-term outcomes of these infants. Subsequently, a few studies in the pre and post-surfactant era reported a reduction in CLD when CPAP was used as the primary treatment strategy for RDS compared with mechanical ventilation (Wung [6], Avery [7], van Marten [8]. However, these were observational studies. Two large randomised controlled trials have since been conducted to assess CPAP as the primary mode of respiratory support in RDS – the COIN and SUPPORT trials.

The COIN (CPAP or Intubation) trial was an international multicentre trial which recruited 610 infants born at 25-28 weeks’ gestation [9]. After birth, infants who required ongoing respiratory support at 5 minutes of age and who were spontaneously breathing were randomised to receive either nasal CPAP started at a pressure of 8 cm of water or intubation and ventilation. In the CPAP group, there were set failure criteria which then warranted intubation and mechanical ventilation. Surfactant treatment was not prescriptive for all ventilated babies but depended on the individual unit’s protocol. Results showed that there was no statistical difference in the primary outcome of death or BPD between the two groups. However, the CPAP group had a lower risk of the combined outcome of death or the need for oxygen therapy at 28 days. Although the CPAP group also had fewer days of mechanical ventilation, a signi-
significant proportion met the criteria for intubation and ventilation within the first 5 days; this pertained to 46% of infants in the CPAP group, that is 55% of infants born at 25 or 26 weeks’ gestation and 40% of those born at 27 or 28 weeks’ gestation. A major side-effect noted was an increased incidence of pneumothorax in the CPAP group, 9% versus 3% in the intubation group. As noted earlier, CPAP was started at 8 cm of water and unfortunately, the airway pressure when the pneumothorax was diagnosed was not recorded.

The SUPPORT trial (Surfactant, Positive Pressure, and Pulse Oximetry Randomised Trial) is another multicentre randomised controlled trial which has compared early CPAP with intubation and ventilation [10]. In this trial, 1316 infants were randomly assigned to receive either CPAP at 5 cm of water in the delivery room or intubation and surfactant treatment within 1 hour after birth. The gestational age of the infants was lower than in the COIN trial, ranging from 24 weeks 0 days to 27 weeks 6 days. Again, there were set failure criteria that would lead to intubation and surfactant delivery in the CPAP group. The results showed that there was no statistical difference in the primary outcome of death or BPD. There was also a high rate of intubation in the CPAP group (83.1%). However, the CPAP group had fewer days of ventilation with more infants in this group being alive and free from mechanical ventilation at 7 days. There was no significant difference in the occurrence of air leak in either group. The use of postnatal corticosteroids to treat BPD was statistically significantly less in the CPAP group ($p < 0.001$).

The differences in the two trials above are that in the SUPPORT trial, all intubated babies received surfactant therapy whereas in the COIN trial, this depended on the individual units’ protocol. Also CPAP was set at 5 cm of water in the SUPPORT trial compared to 8 cm of water in the COIN trial. It is possible that this difference accounts for the difference in the incidence of air leaks between the trials.

These trials support the use of CPAP as a primary strategy in preterm babies with RDS who are spontaneously breathing.

**CPAP and surfactant**

Surfactant therapy combined with mechanical ventilation has been used in babies with RDS since around 1980. Surfactant therapy has been shown to improve mortality and reduce air leak in babies with RDS [11]. There is therefore the hypothesis that CPAP and surfactant combined might be better than CPAP alone.

A number of studies have explored this. Verder et al. conducted the INSURE (Intubation-SURfactant, Extubation) trial [12]. This was a multicentre randomised controlled trial involving 11 neonatal intensive care units in Denmark and Sweden. The team recruited 73 infants of 25 to 35 weeks gestation with moderate-severe RDS who were receiving CPAP. The infants were between 2 and 72 hours of age and were randomised to either receive surfactant followed by brief ventilation or continue to receive CPAP. The trial was stopped early as an interim analysis after recruitment of 54 infants showed a clear benefit in the group treated with surfactant. 85% of babies in the CPAP group were subsequently ventilated within a median of 3 hours after randomisation compared to only 43% of babies in the surfactant group who required re-intubation and ventilation after initial extubation. There were however no significant differences between the 2 groups in the outcomes at 28 days including death, pneumothorax, intracerebral haemorrhage and need for oxygen.

A Cochrane meta-analysis has since looked into early surfactant administration with rapid extubation to nasal CPAP versus nasal CPAP with later rescue surfactant and mechanical ventilation in the treatment of early RDS [13]. This review included six randomised controlled trials (Verder 1994, NICHD 2002, Reininger 2005, Vermont Oxford 2003, Dani 2004, Texas Research 2004). The reviewers concluded that the strategy of early surfactant therapy followed by nasal CPAP compared with later, selective surfactant in infants with RDS was associated with less need for mechanical ventilation (typical RR 0.67, 95% CI 0.57, 0.79), fewer airleak syndromes (typical RR 0.52, 95% CI 0.28, 0.96) and lower incidence of BPD (typical RR 0.51, 95% CI 0.26, 0.99). Meta-analysis also suggested a trend towards decreased mortality in the early surfactant group. A lower treatment threshold ($\text{FiO}_2 < 0.45$) appeared more beneficial for initiation of early surfactant and intubation compared to a higher treatment threshold ($\text{FiO}_2 > 0.45$) for later, selective surfactant therapy and mechanical ventilation.

**CPAP in practice**

CPAP as a primary mode of respiratory support in newborn infants with RDS has proven advantages: no need for intubation or sedative and paralytic agents and less long-term respiratory morbidity. Its use has to be selective in spontaneously breathing infants and so far there is no clear weight or gestational cut-off at which CPAP is more effective. Moreover, failure rate of CPAP leading to mechanical ventilation is high: 46% in the
COIN trial and 83% in the SUPPORT trial. There are uncertainties about what pressure to start and how to wean CPAP support. There is also debate about nasal interfaces and devices. A Cochrane review found that short binaural prongs are more effective than single prongs in reducing the rate of re-intubation [14]. There is a choice of Bubble CPAP, Infant Flow Driver CPAP and ventilator CPAP. Gupta et al found that in babies being extubated after a period of ventilation for RDS, bubble CPAP was associated with less re-intubation than Infant Flow Driver CPAP [15]. CPAP has been shown to be associated with nasal trauma which was not related to the type of CPAP device used [16].

Other strategies

Other non-invasive modes of respiratory support are being trialled such as bilevel positive airway pressure [17], humidified high flow nasal cannula [18] and nasal intermittent positive pressure ventilation [19] with an aim to improve acute respiratory outcome in RDS and reduce long-term respiratory morbidity. Different modes of ventilation including synchronised mechanical ventilation [20] and volume targeted ventilation [21] versus pressure limited ventilation may provide gentler ventilation associated with reduced VILI.

Conclusion

CPAP as a primary mode of respiratory support for babies with RDS is effective in a selected group of infants. More studies are needed looking at optimising CPAP and maximising its benefits while giving us device specific results and effective CPAP treatment protocols.

Practice points

- CPAP is effective in a selected group of infants with RDS.
- Its use reduces the incidence of long term respiratory morbidity.
- Its benefits are enhanced by concomitant administration of surfactant.
- It can be associated with a high failure rate.
- There are uncertainties about which CPAP device is better, optimal pressures to use, weaning regime and best nasal interfaces for CPAP.

References


Sunil Sinha
sunil.sinha@stees.nhs.uk