

Prevention of Ventilator associated complications

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Abbreviations: VAP- Ventilator associated pneumonia , BPD- Bronchopulmonary dysplasia, ELBW- Extremely low birth weight, VLBW- Very low birth weight, ROP- Retinopathy of prematurity, CPAP- Continuous positive airway pressure, I.M.- intramuscular, CI- Confidence intervals, PPRM- Preterm prelabour rupture of membranes, RCT- Randomised control trial, RR- Relative risk, PEEP- Peak end expiratory pressure

Background:

The last two decades have witnessed a dramatic reduction in neonatal mortality from 4.4 million newborn deaths annually in 1990 to 2.9 million deaths yearly in the year 2012, a reduction by 35%. In India, neonatal mortality has decreased by 42% during the same period. (1) With the increasing survival and therapeutic advances, the new paradigm is now on providing best quality of care and preventing complications related to therapy.

Assisted ventilation dates back to 1879, when the Aerophone Pulmonaire, the world's earliest ventilator was developed. This was essentially a simple tube connected to a rubber bulb. The tube was placed in the infant's airway and the bulb was alternately compressed and released to produce inspiration and expiration. (2)

With better understanding of pulmonary physiology and mechanics , lung protective strategies have evolved in the last two decades, with new resuscitation devices that limit pressure (T-piece resuscitator), non-invasive ventilation, microprocessors that allow synchronised breaths and regulate volume and high frequency oscillators/ jet ventilators. (2)

Neonatal ventilation- Trends and numbers in India

The National Neonatal Perinatal database estimates that almost 2.2% of intramural births and nearly 25.6% of extramural admissions require invasive assisted ventilation at some point of time during the neonatal period. (3) The proportion of premature infants needing intubation and ventilation is

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much higher, more so with lower gestation; for example, Kirpalani et al reported that 60% of extremely low birth weight (ELBW) neonates required invasive ventilation. (4) In India, a study from Chandigarh showed that 92% ELBW babies need some form of ventilation and 64% need invasive ventilation during hospital stay. (5)

The availability of ventilators is on the rise in the developing world. A recent survey from India has highlighted that all level II/ III neonatal units surveyed have conventional ventilators, mostly imported and nearly three-fourths have high frequency ventilators. (6) As in any therapeutic modality, ventilation-related misadventures are becoming increasingly common causes of important morbidities in NICU graduates.

Ventilator induced lung injury

The concept of lung injury related to ventilation itself has been recognised as early as 1967 by the use of the term “*respirator lung*” to refer to the pathological changes such as hyaline membranes and diffuse alveolar infiltrates seen in the post-mortem examination of those who underwent mechanical ventilation. (7) Ventilator induced lung injury (VILI) is the net result of excessive airway pressure (barotrauma), tidal volume (volutrauma), flow (rheotrauma), infection and inflammatory mediators (biotrauma) along with repeated opening and closing of alveoli (atelectotrauma).

The complications related to ventilation can be broadly categorized as in panel 1. (2)

Panel 1: Complications of Assisted ventilation (Invasive and non-invasive)

Upper Airway

Nasal septum necrosis
Palatal groove, abnormal dentition
Nasofacial cellulitis (nasotracheal tube)
Subglottic edema/ Tracheal stenosis
Necrotising tracheobronchitis

Lower airway

Ventilator associated pneumonia (VAP)
Bronchopulmonary dysplasia (BPD)
Pulmonary air leak syndromes (pneumothorax, pulmonary interstitial emphysema)
Pulmonary hemorrhage
Atelectasis/ Collapse

Extrapulmonary

Retinopathy of prematurity
Intraventricular hemorrhage
Periventricular leucomalacia

This review will focus on vital strategies related to prevention on BPD, ventilator associated pneumonia and retinopathy of prematurity (ROP).

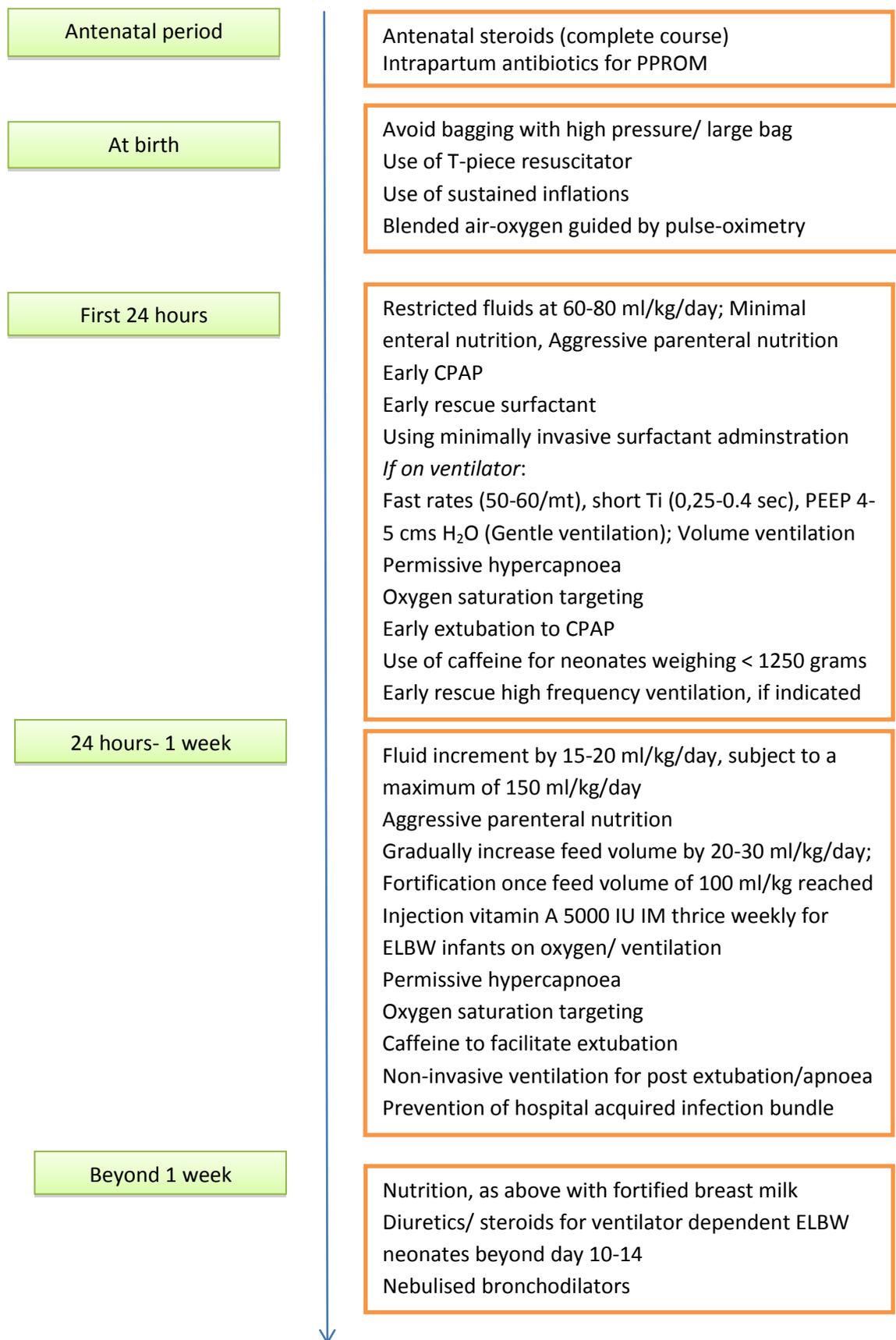
Prevention of bronchopulmonary dysplasia (BPD)

In 1967, Northway reported sequential pathological, clinical and radiological changes in preterm infants who received positive pressure ventilation with high oxygen concentrations in the initial 5 days, which constituted the entity of “*classic BPD*”. (8) With time, the definitions and nomenclature have evolved. In the present era of antenatal steroids, surfactant and less vigorous respiratory support, a milder clinical syndrome of persistent respiratory dysfunction- termed “*new BPD*” is seen predominantly in neonates born below 1000 grams birth weight, characterised pathologically by decrease in alveolar septation, compatible with “*arrested alveolarization*”. (9)

Data from the NICHD network (National Institute of Child Health and Human Development Neonatal Research Network) show that 22% of very low birth weight (VLBW) neonates and almost 34% extremely low birth weight (ELBW) neonates develop BPD. (10) In India, a relatively old study found nearly 50% ELBW neonates to develop BPD. (11) The following figure (Fig. 1) highlights the flow chart of interventions which have been tried in preventing or treating BPD.

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Fig. 1: Flow chart of interventions in prevention / treatment of BPD



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Antenatal strategies

Antenatal steroids: A complete course of antenatal steroids (2 doses of betamethasone 12 mg IM given 24 hours apart or 4 doses of dexamethasone 6 mg IM given 12 hours apart, with at least 24 hours having elapsed after the last dose) reduces risk of death by 31% (95% CI 19-42%), respiratory distress syndrome by 34% (27-41%) and infections in the first 48 hours by 44% (15-62%), but without any significant benefit on BPD. (12) This is probably due to the increased survival of neonates who may have otherwise died before 28 days. Interestingly, antenatal steroids have been found to lower the combined outcome of death or BPD even among neonates born between 23-25 weeks gestation. (13)

Antibiotic prophylaxis for preterm mothers with preterm prelabour rupture of membranes (PROM): Subclinical chorioamnionitis has been increasingly recognised as a risk factor for bronchopulmonary dysplasia. In the landmark ORACLE trial, oral erythromycin 250 mg four times a day for mothers developing PPROM for a duration of 10 days or until delivery resulted in lesser need for oxygen at 28 days (7% vs 8.6%, $p=0.05$). (14) The long term outcomes of these neonates, however was no better than those who received placebo probably due to more prolonged exposure to ongoing in-utero inflammation. (15)

Perinatal strategies

Delivery room (DR) resuscitation- newer understanding- Device: Self inflating bags (SIB), flow inflating bags and T-piece resuscitators can be used to provide positive pressure ventilation (PPV). Although the SIB with an attached PEEP valve can provide PEEP, it is the T-piece which provides consistent and controlled peak inspiratory pressure (PIP), PEEP and CPAP. (16) A randomised trial by Dawson failed to demonstrate a difference in need for intubation between the T-piece resuscitator and SIB. (17)

Sustained inflations: The other advantage of T-piece is that it can be used to provide sustained inflations (SI). Sustained inflations are prolonged breaths with T_i around 10 seconds used to increase the functional residual capacity (FRC). The use of SI was found to reduce need for delivery room intubations from 84% to 40%. (18) TePas conducted a RCT where 207 very preterm infants received either 10-second sustained inflations followed by nasal CPAP or mask PPV using SIB. The first approach was found to reduce intubation within 72 hours, BPD and duration of ventilation significantly. (19) Sustained inflations hold promise to become a simple and safe DR strategy to reduce BPD.

Oxygen concentration: Controversy surrounds the choice of ideal fractional inspired oxygen concentration (FiO_2) to be used during resuscitation in preterm neonates. The ILCOR (International Liaison Committee on Resuscitation) 2010 recommends using blended air oxygen to achieve minute specific target preductal saturations using pulse oximetry in preterm infants. A recent study found that starting from 100% oxygen and rapidly titrating the FiO_2 down every 15 seconds resulted in greater time spent within target saturation targets. All delivery rooms should be ideally equipped with a blender and pulse oximeter in order to optimise FiO_2 used during PPV. (20)

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Postnatal ventilatory strategies

Early Continuous positive airway pressure (CPAP): CPAP recruits alveoli, enhances the functional residual capacity, splints the upper airway and prevents obstructive apnoea. It can be delivered by constant flow systems, such as bubble CPAP and ventilator-delivered CPAP, as well as variable flow systems like infant flow driver and Benveniste (gas jet) valve CPAP.

Observational studies have highlighted the feasibility of nasal CPAP even in ELBW babies, reducing need for intubation without increasing risk of BPD. (21) A large RCT from Australia, in which 610 infants born between 25-28 weeks gestation were randomised to CPAP or invasive ventilation at birth showed no difference in oxygen need at 36 weeks (Odds ratio 0.80, 95% CI 0.58-1.12). Notably, only 46% of neonates who received CPAP required intubation and only 38% required surfactant. (22) Thus, early CPAP should be initiated at the earliest signs of respiratory distress in the delivery room in view of these benefits.

Non-invasive ventilation (Nasal intermittent mandatory ventilation-NIMV): Despite increasing experience, nearly 60% of ELBW neonates fail CPAP. (4) NIMV has been proposed to augment mean airway pressure, reduces thoraco-abdominal asynchrony, reduces work of breathing and increases minute ventilation. (4) A meta-analysis of 3 studies did show NIMV to be better than CPAP in reducing need for invasive ventilation within 72 hours of life, (RR 0.60; 95% CI, 0.43-0.83) although this advantage did not translate into lesser risk of BPD. (23) A large RCT also concluded no added benefit of NIMV over CPAP in long term pulmonary outcomes. (24)

NIMV appears to offer more promise in the setting of apnoea (25) and post-extubation (26) by providing positive pressure breaths non-invasively in neonates with diminished respiratory drive and reducing extubation failure.

Patient triggered ventilation: A major drawback with mandatory ventilation is ventilator - patient asynchrony. The ability to detect spontaneous breathing by change in airway flow (flow sensors) or pressure (pressure sensors) has resulted in synchronised ventilatory modes such as SIMV (synchronised intermittent mandatory ventilation), assist control (AC) and pressure support (PSV) mode. Although these modes theoretically reduce asynchrony, studies have only shown these modes to lessen duration of ventilation by nearly 35 hours without any effect on BPD. (27) Considering that even brief positive pressure ventilation is potentially dangerous, this seems enough ground for opting for synchronised modes wherever resources permit.

Volume ventilation: The major disadvantage in pressure limited ventilation is variable tidal volumes due to rapid changes in compliance, especially hyperventilation and volutrauma. Newer ventilators have volume target ventilation (VTV) using microprocessor driven algorithms to limit peak inspiratory pressure, and resultant hyperventilation as well as hypocarbia. Indeed, VTV has been shown to result in lesser BPD as compared to pressure controlled ventilation (RR 0.61; 95% CI 0.46 to 0.82, p=0.0008), in addition to reduction in ventilation duration by 2 days, lesser risk of intraventricular hemorrhage, pneumothorax, hypocarbia, periventricular leukomalacia and failure of extubation. (28) Clearly, volume ventilation is ideal and preferable if available.

Elective high frequency ventilation (HFV): The elective use of HFV has not been found to offer any benefit over conventional ventilation in reduction of BPD. (29) There may be some benefit of early

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rescue HFV started before 4 hours of life, when conventional ventilation fails and in infants with air leaks.

Permissive hypercapnoea: This refers to a strategy of allowing PaCO₂ to climb to 45-55 mm Hg, provided the pH remains > 7.25 in an attempt to limit excessive tidal volumes and allow adequate PEEP to recruit alveoli. In a multicentre trial, this strategy was found to reduce need for ventilation at 36 weeks, among ELBW infants (1% vs 16%). But potential harms of this strategy include a reduction in alveolar O₂ concentration, increased risk of pulmonary vascular hypertension and retinopathy of prematurity. (30)

Non-Ventilatory strategies

Surfactant replacement therapy: Surfactant therapy can be prophylactic (given to all infants born below 28 weeks gestation before 15 minutes of life without waiting for onset of respiratory distress syndrome [RDS]) or rescue (surfactant replacement in established RDS). Prophylactic surfactant has not been found to reduce BPD in the era of antenatal steroids and early CPAP. (31)

On the other hand, early rescue surfactant therapy within 2 hours of life for neonates with established RDS is associated with lesser risk for air leaks, mortality and BPD/death at 36 weeks (RR 0.84, 95%CI 0.75, 0.93). (32) An Indian study from Hyderabad demonstrated that early routine surfactant administration within 2 hours of life significantly reduced the need for ventilation among preterm infants born before 33 weeks when compared to late selective surfactant. (33) Thus, it may be reasonable to start preterm neonates on CPAP at the earliest signs of RDS and administer surfactant if they continue to require FiO₂ > 0.4 or need ventilation for apnoea/ respiratory acidosis.

There is more interest in alternate routes of surfactant to avoid intubation and PPV, particularly minimally invasive surfactant through a vascular catheter or feeding tube. (34) The catheter is used to instil surfactant through the glottis while continuing CPAP.

Caffeine: Caffeine/ aminophylline has been used for treatment of apnoea and in routine peritubation care. A large multicentre RCT among neonates born between 500-1250 grams birth weight showed caffeine to reduce BPD from 47% in the control group to 36% in the treatment group. The unexpected finding was possibly due to a reduction in duration of ventilation, CPAP and oxygen evidenced in the trial. (35) Caffeine is indicated in very preterm infants for treatment of apnoea as well as after extubation.

Vitamin A: Vitamin A is essential for epithelial integrity and deficiency has been often associated with prolonged oxygen dependency. (36) Despite modest benefit in BPD (RR 0.93; 95% CI: 0.88 to 0.99) mostly driven by Tyson's large RCT in ELBW infants, the efficacy remains questionable in the modern era of aggressive nutrition. (37) Intramuscular administrations in these smallest of infants thrice weekly for 4 weeks also remain unsafe and tedious.

Postnatal steroids (PNS): Steroids have been found to decrease all pathological mechanisms in BPD – inflammation, fibrosis, secondary surfactant inactivation and bronchoconstriction. But early use of postnatal steroids (before 8 days) has been associated with an increased risk of complications such as gastrointestinal bleed/ perforation, hypertension and poor somatic growth. (38) Late postnatal steroids (administered beyond the first postnatal week) have been found to increase the benefits without increasing toxicity / neurological problems. (39) It may be wise to reserve the use of PNS to

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ventilator dependent ELBW infants beyond first week after ruling out other causes of ventilator dependency, and restrict it to the shortest and smallest dose possible. (40)

Oxygen: Exposure to ‘liberal’ oxygen has been implicated in causing BPD for very long. Two RCTs showed that targeting saturation of > 95% were associated with greater need for oxygen at 36 weeks, need for postnatal steroids/ diuretics for BPD and re-hospitalisations for exacerbations of BPD, than a conservative approach. (41,42) Evidence from the neonatal collaborative prospective meta-analysis expressed concerns over increased mortality (RR 1.45; 95% CI 1.15–1.84) among those neonates randomised to saturation targets below 90%, based on data from UK, Australia and New Zealand after revising the calibration of Masimo pulse oximeters used in the trials. (43) Until consensus is reached, it may be safe and optimal to target saturations of 91-95% in the initial weeks of life upto 36 weeks post conceptional age.

Fluid restriction: A systematic review by Bell suggests that restricting fluid intake in the first week to 10 days of life is associated with lesser risk of PDA, NEC and a trend towards lesser BPD (RR 0.85 [0.63, 1.14]), with the disadvantage of greater postnatal weight loss. The precise delineation between liberal and restricted fluids is contentious, with studies quoting average intake of 122 ml/kg/day in the “restrictive” vs 169 ml/kg/day in the “liberal” group. (44)

Nutrition: Aggressive nutritional strategies include minimal enteral nutrition once the infant is hemodynamically stable, daily feed increment by 15-20 ml/kg/day in ELBW babies, early (< 24 hours) and aggressive parenteral nutrition (amino acid up to 3-5-4 g/kg/day), continued PN till feed volume of at least 130 ml/kg/day and feeding human milk only (with fortification in VLBW neonates). Although not directly proven, there is sufficient rationale that adequate nutrition is necessary for continued lung growth and maturation. (45)

The role of other therapies like inhaled steroids, diuretics, mast cell stabilisers, anti-oxidants like vitamin E and superoxide dismutase are currently not backed by sufficient evidence.

Interventions to reduce air leaks

Air leaks in neonates occur more often in the compliant terminal bronchioles rather than the non-compliant unexpanded more distant saccules, thereby, pulmonary interstitial emphysema is more common than pneumothorax. Strategies to prevent air leaks include minimizing peak inspiratory pressure, using short inspiratory times and reduce distending pressure. (2) A promising ventilatory strategy to reduce the risk for air leaks is volume ventilation. There is a place for high frequency ventilation in established air leaks, especially high frequency jet ventilation.

Prevention of ventilator associated pneumonia (VAP)

The panel 2 summarises interventions useful in reducing ventilator-associated pneumonia (HAI). Recently, Indian neonatologists from Hyderabad have devised a checklist of interventions to prevent hospital acquired infections and procedure related complications, including VAP.

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Panel 2: Interventions useful in preventing ventilator associated pneumonia

Interventions useful in preventing ventilator associated pneumonia:

- Education of staff and involvement in infection prevention
- Collation of infection and microbiological surveillance trends in health care associated pneumonia
- Prevention of person to person transmission :
 - Hand hygiene, appropriate disinfection, barrier nursing, avoidance of keeping ventilator tubes “stand-by” for > 12 hours, avoidance of condensation in inspiratory tubing
- Modification of host susceptibility:
 - Removal of endotracheal, tracheostomy tube at the earliest, head elevation (30-45 degrees) , oral hygiene, avoidance of H₂ blockers

Some specific strategies which have been attempted are:

Position of the head/body: The CDC recommends that in the absence of medical contraindications, the head end of a ventilated neonate should be placed 30-45° higher than the plane of the body. (46) It would also be preferable to place the endotracheal tube and ventilator circuit in horizontal position to prevent tracking of secretions and non-supine better is associated with lesser chance of VAP. (47)

Suctioning: The use of in-line or closed suctioning has been found to reduce the episodes of hypoxia and bradycardia in unstable babies especially on HFV. Although it reduces chances of environmental contamination of the endotracheal tube, there may be re-introduction of pooled secretions in the lumen of the suction catheter into the lungs. Adult studies have found equal or slightly lesser rates of VAP with closed suction systems. (46) Adequate hygiene, knowledge about the size of catheter to be used and depth of insertion, limiting negative pressure to not more than 5 seconds and avoidance of indiscriminate use of saline are other important considerations. Nasal suction before oral suction, avoidance of bulb suction and reusable catheters are to be ensured. (48)

Oral decontamination: Oral care with toothbrush and oral application of chlorhexidine antiseptic gel twice daily has been tried in children with the aim of reducing VAP, with unfavourable results. There is currently insufficient evidence to recommend any of these interventions for neonates. (46)

Interventions to reduce upper airway complications:

The prevention of CPAP related nasal injury relies on careful attention to the prevention of pressure, friction and moisture. The list of useful nursing intervention in the prevention of nasal injury as well as endotracheal tube related upper airway complications is listed below:

1. **Choice of correct sized interface and fixation:** Excessively large sized prongs may cause mucosal injury, while smaller prongs may frequently dislodge, leading to perpetuation of injury.

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2. **Optimal humidification:** Regular instillation of saline drops during CPAP and meticulous attention to proper heating and humidification cannot be understated.

3. **Choice of nasal interface:** There is atleast one RCT which found that the mean age of onset of nasal injury was delayed with the use of nasal masks for delivering CPAP, as compared to binasal prongs. (49) The use of specific adhesive material (E.g., cannulaide) to improve seal and prevent trauma is seen as an innovation in fixing the interface.

4. **Steroids to prevent subglottic edema:** A meta-analysis of 3 RCTs recommends the use of a short course of dexamethasone to prevent glottis edema and reduce extubation failure in a group of neonates ventilated for > 7 days and with multiple extubation failures. (50)

Interventions to prevent extra-pulmonary complications

Retinopathy of prematurity: The risk of severe ROP is lesser with lower oxygen saturation targets (85-89%) as opposed to higher targets (91-95%) [RR 0.52, 0.37-0.73] but at the cost of increased mortality (19.9% vs16.2%). (42) From available evidence, it is clear that targeting higher oxygen saturations in the initial weeks of birth result in an increased rate of severe ROP needing treatment. A meticulous analysis of oxygenation patterns with a closed loop system oxygen analyser may be the way forward in this regard.

Intraventricular hemorrhage/ Periventricular leukomalacia: The risk factors for IVH include asynchrony, use of excessive pressures, air leaks and sudden fluctuations in PaCO₂ (partial pressure of carbon-dioxide). More prolonged exposure to hypocapnoea increases risk of PVL by nearly 5 times (7.4% vs 1.4%). As in prevention of BPD, the importance of gentle ventilation with minimal tidal volumes and prevention of hypocapnoea is essential. The use of volume targeted ventilation has been found to reduce IVH (RR 0.65, 95% CI 0.42 to 0.99) and periventricular leucomalacia (RR 0.33, 95%CI 0.15 to 0.72) as compared to pressure controlled ventilation. (28)

Conclusions

The purpose of ventilation is ultimately to get out of it as early as possible. Preventing ventilator related complications by gentle ventilatory strategies, permissive hypercapnoea, appropriate use of non invasive ventilation, patient triggered and volume targeted ventilation wherever possible, targeting saturations between 91-95% is the current standard of care. Exogenous rescue surfactant treatment, with novel delivery methods under evaluation, caffeine and aggressive nutrition with restricted fluids are also supported by evidence.

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