CHAPTER

2

CPAP - Evidence for use

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Continuous Positive Airway Pressure (CPAP) is the most common form of non-invasive respiratory support applied to preterm infants and is a standard of care. It was first used in preterm infants in 1971[1]. After the introduction of surfactant into the therapeutic armamentarium, the thrust shifted to new and sophisticated ventilation strategies in the management of respiratory distress syndrome in newborns. Nevertheless, chronic lung disease (CLD) remained a frequent sequel of prematurity. Ventilation itself was identified as the most important cause of CLD[2]. The term "ventilator-induced lung injury" (VILI) implies that lasting damage may be avoided if VLBW infants can be prevented from being ventilated. "VILI" stimulated the reinvention of CPAP as a gentler and effective mode of respiratory support. Renowned institutions in New York and Scandinavia have practiced primary nasal CPAP in very preterm infants for three decades, resulting in less usage of surfactant and ventilation and impressively low rates of CLD[3]. Today the use of CPAP has spread widely across most units in our country and there is an increasing variety of devices, interfaces and approaches. Use of early CPAP has been shown to be one of the four evidence based practices which has resulted in increased survival without severe morbidity among very preterm infants[4]. This review provides some perspectives on this increasingly complex debate surrounding CPAP and its further development.

How does CPAP work?

CPAP supports the breathing of premature infants in a number of ways. The upper airway of the preterm infant is very compliant and therefore prone to collapse. CPAP splints the upper airway and therefore reduces obstructive apnoeas[5] Moreover it stimulates 'J' receptors by stretching the lung and pleura and decreases diaphragmatic fatigue, thus is useful in treating apnea of prematurity.

Preterm infants struggle to establish and maintain lung volumes due to surfactant deficiency, muscle hypotonia, slow clearance of lung fluid and a compliant chest

wall. CPAP assists expansion of the lungs and prevents alveolar collapse. In doing so it reduces protein leak and also results in better pneumocyte II function and conserves surfactant, thus contributing to early recovery from RDS[6].

CPAP devices

CPAP has been applied to preterm infants using an array of devices. Gregory used it by enclosing the head in a plastic pressure chamber[1]. Subsequent CPAP devices included a pressurized plastic bag fitted over the infant's head, face chamber and face masks. The use of facial masks and devices requiring a neck seal declined as a consequence of serious complications and difficulty in maintaining an adequate seal. The most common interfaces used for CPAP are nasal prongs and nasal masks. Nasal prongs can be short (6-15 mm) or long (40-90 mm), and single or binasal. The long nasal prongs which are actually nasopharyngeal prongs have the disadvantages of high resistance, more prone to kinking and blockage by secretions, and difficulty in monitoring local side effects. The short binasal prongs include Argyle, Hudson, Medicorp, Fisher & Paykel prongs and IFD prongs. Short binasal prongs have the least resistance to flow and are more effective at preventing re-intubation than single nasal or nasopharyngeal prongs [RR 0.59; 95% CI: 0.41, 0.85] in preterm neonates[7]. In patients with RDS, short binasal prongs were found to be superior to nasopharyngeal prongs in terms of lower oxygen requirement and lesser respiratory rate in first 48 hours[8]. A study comparing Hudson with Argyl prongs in preterm neonates, receiving nasal CPAP as initial ventilatory assistance or for weaning from a ventilator, concluded that Argyle prong is more difficult to be retained inthe nostrils of active patients and nasal hyperemia occurs more frequently with its use[9]. Few RCTs have compared nasal prongs with nasal masks and have shown promising results. In a RCT among VLBW neonates, comparing nasal prongs with nasal mask, no significant difference was noted in the incidence of nasal injury[10]. Another randomized trial in neonates <31 weeks gestation comparing nasal mask with binasal prongs showed less intubation rate within 72 hours for the treatment of RDS or in post-extubation setting with nasal mask (28% *vs* 52%; *P*=0.007)[11]. **Çhandrasekaran et al** from India reported a 6% reduction in the oxygen requirement at 2 hours of CPAP initiation with nasal mask as compared to nasal prongs. Moreover, infants on nasal mask had no nasal injury (31.3% *vs* 0%; *P* = < 0.01). On post-hoc analysis, the need for surfactant after starting CPAP was markedly lesser (95% CI 33% - 89%, *P*<0.01) in the nasal mask group[12]. Another trial from India by Goel et al comparing nasal mask with prongs among preterm neonates of 27-34 week gestation requiring CPAP as a primary mode of respiratory distress found no statistically significant difference in the need for mechanical ventilation within first 72 hours of initiating

CPAP, however; the rate of pulmonary interstitial emphysema (4.9% vs. 17.5%; RR 0.28, 95% CI 0.08-0.96; P = 0.03)incidence of moderate nasal trauma (6.5% vs 21%) (P=0.03) and overall nasal trauma (36% vs 58%) (P=0.02) was significantly lower in mask group than in the prongs group[13]. Thus, the initial results are encouraging primarily in terms of reducing nasal trauma however, more evidence is required before nasal masks can replace short binasal prongs.

'RAM cannula' is a binasal prong like the oxygen prongs but with a diameter much wider than the conventional oxygen prongs. It is easy to apply and retains the benefit of a circuit with inspiratory and expiratory limbs to provide non-invasive ventilation. Preliminary data is promising but more evidence is required to support its use[14]. Nzegwu, et al[15] in a recent prospective observational study showed that RAM cannula was well tolerated in neonates. The overall success rate in weaning off the RAM cannula was 66% in newborns who were on CPAP with FiO2 $\leq$0.35[15].

Techniques for pressure generation

Expiratory flow valve (e.g. ventilator)

The ventilator PEEP valve controls the CPAP delivered. The flow is usually set to about 4-6 L/min. If the flow is too low or if there are large leaks, adequate pressure will not be delivered and the work of breathing may be increased. The work of breathing was found to be increased with conventional ventilator driven CPAP (circuit flow limited to 6 L/min) compared with an IFD system maintaining pressure at the device level with variable flow.

Underwater tube 'bubble' CPAP

Underwater bubble CPAP remains in use since first devised in the early 1970's[1]. With this technique gas flows past the nasal device and the pressure is generated in the circuit by placing the distal limb of the CPAP circuit under a known depth of water. This is a simple and effective technique which can be applied with inexpensive equipment. A unique feature is that loss of CPAP pressure is detectable by the disappearance of the bubbling. A comparison of underwater bubble endotracheal (ET) CPAP with ventilator derived ETCPAP in preterm neonates suggested that the bubbling contributed to gas exchange.

Bubble CPAP produces pressure oscillations of up to 4 cm H_2O measured in the circuit. It has been suggested that bubble CPAP is more effective than ventilator CPAP because of these oscillations[16]. However, Kahn et al. showed that bubble CPAP pressure oscillations are progressively attenuated distal to the prongs[17]. This suggests that very little effect of the

oscillations will be transmitted to the periphery of the lungs. An in-vitro study suggests that the noisy pressure waveform of bubble CPAP superimposed on pressure fluctuations as a result of spontaneous breathing may promote airway opening events as a result of stochastic resonance[18]. Short-term cross-over study of human neonates comparing fast bubbling with minimum bubbling did not find any difference in blood gases.[19] Di Blasi et al showed that changing the angulation of the tip of the submerged expiratory limb may amplify the oscillatory pressure amplitude and further enhance gas exchange efficiency[20]. Preterm lamb model compared bubble CPAP with ventilator-generated CPAP and found that the bubble technique was associated with a slightly higher pH, better oxygenation and decreased alveolar-exuded protein, compared with the ventilator group[21]. In a randomized cross over design among very low birth weight infants, there was no significant difference in work of breathing, tidal volume, respiratory rate, heart rate and breathing asynchrony between bubble CPAP and ventilator CPAP but the transcutaneous oxygen was higher in the bubble CPAP group[22]. A study comparing bubble CPAP with variable flow CPAP in VLBW neonates with minimal respiratory distress showed that the breathing may be more labored and asynchronous with bubble NCPAP and this may lead to higher failure rates[23]. Tagare et al in a pilot RCT showed that the success rate of bubble CPAP was same as that of ventilator CPAP in preterm infants with respiratory distress when CPAP was started within 6 hours of life[24]. Another pilot RCT found that the bubble CPAP was associated with 50% reduction in the extubation failure rate though the difference was not statistically significant[25].

Variable flow nasal CPAP devices

These devices have an integrated nasal interface and pressure generator and use a higher gas flow than other devices. The most commonly used device is the IFD system. Pressure in the system is created at the level of the nasal device ('Generator') to which short binasal prongs are attached. The pressure generated in this device is controlled directly by adjusting the flow and flows of 8 L/min or more are needed to generate pressures of 5 cm H_2O or more. The "expiratory" limb of the IFD is unusual among CPAP devices in that it is open to the atmosphere. Potentially, the baby can inspire with a higher flow than that is flowing through the inspiratory limb. This extra gas flow can be drawn from the expiratory limb ("variable flow"). This reduces the possibility of the pressure falling with large inspirations and therefore may reduce the work the baby expends to take large breaths. Similarly, the infant can expire with lesser work into this open tube which decreases the resistance.

Inspite of widespread popularity of IFD, few clinical data are available to substantiate its

clinical superiority over other devices. In a short-term cross-over study of 20 neonates receiving 30% oxygen, Ahluwalia et al compared single-prong NCPAP with the IFD. They found no significant differences in FiO_2, respiratory rate, heart rate, blood pressure or comfort score of infants[26]. But in 2001, an RCT of 36 preterm infants comparing IFD with nasopharyngeal bubble CPAP found that the IFD group had significantly improved oxygenation and respiratory rates[27]. In the same year, Courtney et al showed that in premature infants with mild respiratory distress, measured lung volumes were significantly higher with the IFD compared to the INCA prongs and nasal cannula[28]. In 2007, Boumecid et al found that the IFD increased tidal volume and improved thoraco-abdominal synchrony compared with bi-nasal CPAP and nasal cannula, in preterm infants[29]. Pantalitschka et al in a randomized cross over study showed that the cumulative event rate of bradycardia and desaturations per hour were significantly less with variable flow CPAP as compared to bubble CPAP in preterm infants receiving CPAP for apnea of prennaturity[30]. However, in a multicentric RCT among preterm infants weighing 750-1500 grams, the treatment failure was not statistically different between the variable flow CPAP and ventilator CPAP[31]. Similarly in another RCT, variable flow CPAP showed the same benefits (CPAP failure rate, total CRAP duration, total oxygen duration) as bubble CPAP in newborns with birth weight 1500 grams and receiving CPAP for moderate respiratory distress within first 24 hrs after birth[32]. In experimental study, noise production measured in a closed incubator at 2 mm lateral distance from the end of the nasal prongs was found to be significantly more with variable flow CPAP as compared to constant flow CPAP generators[33].

Various studies comparing variable flow CPAP with constant flow CPAP generators in the post extubation setting have also shown mixed results. Roukema et al and Sun et al 1999 in two separate studies showed less extubation failure rate with variable flow CPAP. In a recent RCT in 2009, 140 preterm infants at 24 to 29 weeks' gestation who were ventilated at birth for RDS were randomized to receive either IFD CPAP or bubble CPAP with the primary outcome being the successful extubation maintained for at least 72 hours. The authors found that the IFD and the Bubble CPAP were equally effective in the post-extubation management of infants with RDS. But in those infants who were ventilated for < 14 days, bubble CPAP was associated with a significantly higher rate of successful extubation and reduced duration of CPAP support[34]. Stefanescu et al found no import and differences in rates of extubation failure in ELBW infants between IFD and INCA prongs[35]. An analysis of studies so far show that unequivocal clinical superiority of IFD over less expensive constant flow systems has not yet been demonstrated.

Arabella is another variable flow nasal CPAP system. A comparison study between IFD and Arabella in VLBW infants with mild respiratory distress showed no difference in lung volume recruitment, work of breathing, compliance, tidal volume, respiratory rate, and minute ventilation between the two devices[36].

The Benveniste valve is a technically simple device consisting of a constant gas jet directed through a ring towards the connection with the nasal interface[3]. A high gas flow of 8 to 14 L/min is required to create a pressure of between 5 and 10 cm H_2O in the oro-pharynx. Despite being a relative simple and inexpensive device it has not gained popularity outside the scandinavian countries though it is now available in our country. In a recent two-site RCT comparing Benveniste valve (Jet CPAP) with bubble CPAP in neonates with respiratory distress, there was no difference in the failure rate (40% vs 43%, p=0.8), mortality or any other morbidity between the two groups. The prong displacements were more common with Benveniste valve (Jet CPAP) [Median (range): 3 (0,20) versus 1 (0, 12); p=0.004] as compared to bubble CPAP. However, the neonates were more comfortable with Benveniste valve with the median (IQR) pain score assessed by N-PASS being 3 (3,4) as compared to 4 (3,5) in bubble CPAP group (p=0.01)[37].

High flow nasal cannulae

Simple nasal cannulas with an outer diameter of 3 mm and flows up to 2 L/min, have been reported to deliver CPAP. Heated Humidified High-flow Nasal Cannula (HHHFNC)are another potential form of non-invasive support where warm and humidified respiratory gases (close to 37°C and 100% relative humidity) are delivered at flow rates between 2 to 8 L/min. HHHFNC reduces work of breathing through multiple mechanisms including decreasing inspiratory resistance, washing out nasopharyngeal dead space and providing positive airway distending pressure. It has been tried as primary respiratory support soon after birth and in post-extubation setting. However, in case of tightly fitting nasal prongs and high flow rates, HHHFNC can generate high pressures in airway which may cause airway desiccation and mucosal injury. Few RCTs have been conducted in last one decade which have tried to assess the efficacy and safety of HHHFNC especially in comparison to nasal CPAP. The updated cochrane review[38]found that when used as primary respiratory support after birth compared to CPAP (4 studies, 439 infants), there were no differences in the primary outcomes of death (RR 0.36, 95% CI 0.01 to 8.73; 4 studies, 439 infants) or chronic lung disease (CLD) (RR 2.07, 95% CI 0.64 to 6.64; 4 studies, 439 infants). However, HHHFNC use resulted in longer duration of respiratory support.A large multicentric RCT (HIPSTER

trial) done after the updated Cochrane review enrolled infants between 28-36 weeks of gestation (n=564) and compared HHHFNC with nCPAP as a primary means of respiratory support for preterm infants with early respiratory distress. The trial recruitment stopped early because of a significantly higher treatment failure in HHHFNC group as compared to nCPAP group (71 of 278 infants (25.5%) vs. 38 of 286 infants (13.3%; RD 12.3, 95% CI 5.8 to 18.7; P<0.001). Moreover, the median duration of respiratory support was 1 day longer in the HHHFNC group as compared to nCPAP group (4 vs. 3 days, P=0.005). However, the rate of intubation within 72 hours did not differ significantly between the two groups[39].

Following extubation (total 6 studies, 934 infants), there were no differences between HHHFNC and CPAP in the primary outcomes of death (typical RR 0.77, 95% CI 0.43 to 1.36; 5 studies, 896 infants) or CLD (typical RR 0.96, 95% CI 0.78 to 1.18; 5 studies, 893 infants). There was no difference in the rate of treatment failure (typical RR 1.21, 95% CI 0.95 to 1.55; 5 studies, 786 infants) or reintubation (typical RR 0.91, 95% CI 0.68 to 1.20; 6 studies, 934 infants). However, infants randomised to HHHFNC had reduced nasal trauma (typical RR 0.64, 95% CI 0.51 to 0.79; typical risk difference (RD) - 0.14, 95% CI - 0.20 to - 0.08; 4 studies, 645 infants). Thus, HHHFNC has a potential role as an alternative to CPAP in post-extubation setting due to less nasal trauma and its ease of application. None of the studies have been powered to determine the safety of HHHFNC[39]. The same has been reiterated by AAP[40]. Therefore, careful attention should be given to the size of the prongs and lowest effective flow rates should be used while applying HHHFNC.

Table I : Studies comparing various types of Constant flow pressure generators

Author	Study Design	Study population	Comparison	Results
Lee et al 1998	Randomized with crossover design	N=10 750-2,000 g Preterm neonates ready for extubation	Bubble CPAP vs Ventilator CPAP	39% reduction in infant's lung volume and 7% reduction in respiratory rate but no difference in blood gas parameters in infants on BCPAP
Pillow et al 2007	Experimental (lamb model)	N=34 Preterm lambs treated with CPAP for 3 hours	Bubble CPAP vs Ventilator CPAP	Bubble CPAP was associated with a higher pH, PaO_2, oxygen uptake, and a decreased alveolar protein & ventilation inhomogeneity
Tagare et al 2010	RCT (pilot study)	N=30 Preterm (<37w k) neonates with respiratory distress and oxygen requirement >30% in first 6 h of life	Bubble CPAP vs Ventilator CPAP	Success rate and dislodgement rate were comparable
Courtney et al 2011	Randomized with crossover design	N=18 Neonates <1500 grams and <28days old and on NCPAP for mild respiratory distress	Bubble CPAP vs Ventilator CPAP	No significant difference In work of breathing, tidal volume, respiratory rate, heart rate, breathing asynchrony but transcutaneous oxygen was highper with Bubble CPAP
Yadav et al 2012	RCT (pilot study)	N=32 Neonates < 32 and <1500grams	Bubble CPAP vs Ventilator CPAP	BCPAP was associated with 50% reduction in the extubation failure rate though the difference was not statistically significant
Tagare, *et al*, 2013	RCT	N=114, Neonates <37 weeks with respiratory distress within 6 h and Silverman-Anderson score≥4 and oxygen requirement >30% within first 6 h of life	Bubble CPAP vs Ventilator CPAP	Bubble has higher success rate than ventilator CPAP (82.5% vs 63.2%; p =0.03)

Table II: Studies on CPAP using Infant Flow Driver

Author	Study Design	Study population	Comparison	Results
Moa et al 1988	Experimental in vitro study	Lung model simulated breathing pattern of a newborn	Variable flow NCPAP vs Continuous flow NCPAP	Pressure variations in airway and external workload were less with variable flow CPAP device
Klausner et al 1996	Experimental in vitro study	Breathing apparatus simulating breathing pattern of a VLBW newborn	Variable flow NCPAP vs Continuous flow NCPAP	Imposed work of breathing and variations in airway pressure was less with NCPAP device variable flow
Ahluwahalia et al 1998	Crossover study	N=20, Infant of 24-34 weeks on CPAP with FiO_2 of 0.3.	IFD vs single prong ventilator NCPAP	No significant difference in respiratory rate, heart rate, blood pressure and comfort score Oxygen requirement and respiratory rate
Pandit et al 2001	Crossover trial	N=24; <1800gms receiving constant flow NCPAP for apnea or mild respiratory distress	Infant flow system NCPAP vs ventilator NCPAP	Work of breathing lower with variable flow (13 to 29%) as compared to ventilator CPAP Liptsen et
Mazella et a 2001	RCT	N=36 RDS in <36 weeks infants and <12 hours old	IFD vs nasopharyngeal bubble CPAP	significantly decreased by four hours. Probability of remaining supplementary oxygen free over the first 48 hours of treatment significantly higher in patients treated with the IFD.
Courtney et al, 2001	Crossover study	N=32; birth weight 1081±316, 29±2 weeks receiving nCPAP for apnea or mild respiratory distress were enrolled at the age of 13±12 days	IFD vs Ventilator CPAP via CPAP prongs vs Ventilator CPAP via modified nasal cannula	Compared with two continuous flow devices, the variable flow nasal CPAP device leads to greater lung recruitment
Liptsen et al 2005	RCT	N=18; <1500gm birth wt. <28 days of age, requiring NCPAP for mild respiratory distress	IFD vs Bubble NCPAP	Resistive work of breathing, respiratory rate and phase angle (time lag between chest and abdominal movement) were all greater with bubble compared to IFD

Boumecid et al 2007	Crossover study	N=13; 26-32weeks All were evaluated on each device applied for 30 minutes in random order	Variable-flow NCPAP, continuous flow NCPAP and nasal cannula	Variable-flow NCPAP increases tidal volume and improves thoraco-abdominal synchrony
Pantalitschka et al 2009	Crossover trial	N=16, 31 weeks; all infants having apnea of prematurity were allocated to four different modes of respiratory support for 6 h each	NIPPV via a conventional ventilator vsNIPPV via a variable flow devicevsNCPAP via a variable flow devicevsNCPAP via a constant flow underwater bubble system	The median event rate [cumulative event rate of bradycardias (< or =80 beats per minute) and desaturation events (< or =80% arterial oxygen saturation] was significantly less with variable flow CPAP as compared to bubble CPAP (2.8 per hr vs 5.4 per hr)
Yaqui et al 2011	RCT	N=40 > 1500 gms (mean birth weight 2500 gms) with Fi02 > 30% within first 24 hrs after birth (70% of subjects had TTNB)	Variable flow CPAP vs Bubble CPAP	Bubble CPAP showed the same benefits (CPAP failure rate, total CPAP duration, total oxygen duration) as variable flow CPAP in newborns with birth weight 1500 grams and moderate respiratory distress
Bober K et al 2012	Multicentric RCT	N=276, infants with birth weight 750-1500g and 32 wks were divided into 'weaning group' (infants that met criteria for intubation and surfactant) and 'elective group'(infants that did not meet intubation criteria but required respiratory support within 6 hrs of delivery) and then were randomly assigned intervention	Infant flow CPAP vs ventilator CPAP	Treatment failure (defined as the need for reintubation and mechanical ventilation within 3 days of initial extubation in the 'weaning group' and need for intubation in the first 3 days after first weaning from NCPAP in the 'elective group') was not statistically different in the two groups
Kirchner et al 2012	Experimental in vitro study	Noise production was measured in a closed incubator at 2 mm lateral distance from the end of the nasal prongs in an experimental model	Variable flow CPAP generator (Infant flow and Medijet) vs constant flow CPAP generator (Bubble CPAP and Baby flow ventilator CPAP)	Values measured at a continuous constant flow rate of 8 1/min averaged 83 dB for the Infant Flow, 72 dB for the MediJet, 62 dB for the Bubble CPAP and 55 dB for the Baby Flow. Constant flow CPAP generator work more quietly than the variable flow CPAP generators

Table-III: Use of IFD in post - extubation setting

Author	Study Design	Study population	Comparison	Results
Roukema et al 1999	Crossover trial	N=93; 1250gms Used as post extubation respiratory support to decrease extubation failure	Infant flow NCPAP vs nasopharyngeal CPAP	Less extubation failure with IFD CPAP
Sun et al 1999	RCT	N=73; <1250gms Had RDS and were mechanically	Flow driver CPAP vs conventional NCPAP	Extubation failure rate was higher in conventional NCPAP on Day 1 and within 7 days of extubation ventilated
Kavvadia et al 2000	RCT	N=36; 25-35 weeks 12 infants in each group after extubation were put on IFD or single nasal prong NCPAP or no CPAP	IFD or single nasal prong NCPAP or no CPAP	IFD offered no short term advantage over single nasal prong NCPAP when used after extubation
Stefanescu et al 2003	RCT	N=162; 1000gms Used as post extubation respiratory support to decrease extubation failure	Infant flow NCPAP vs Ventilator NCPAP	IFD CPAP was as effective as ventilator CPAP in preventing extubation failure
Huckstadt et al 2003	Randomized cross over Trial	N=20, 26-40 weeks; 640-4110gms; Being mechanically ventilated for TTNB, RDS, sepsis	Infant flow CPAP vs Ventilator CPAP	There was a significant increase in the inspiratory flow and tidal volume and less fluctuations in CPAP pressures during the breathing cycle with Infant flow system
Gupta et al 2009	RCT	N=140, 24-29wks; 600-1500gms Had RDS and were mechanically ventilated	Bubble CPAP vs IFD	Bubble CPAP was as effective as IFD CPAP. Bubble CPAP was associated with a significantly higher rate of successful extubation in infants ventilated for < 14 days, and a significantly reduced duration of CPAP support

Practical problems of NCPAP

Fixation of nasal devices

There are many different techniques for fixing the devices to the infant. The exact technique does not matter as long as the device is secure and not traumatizing the nose, face, or head. More research is needed to define the least traumatic nasal device and method of fixation.

Leak at the nose and mouth

Nose and mouth leaks are inherent problems with any CPAP delivery device and the set CPAP level is rarely maintained in the pharynx[41]. Best ways to reduce nose leak are to ensure the usage of a snugly fitting prong without causing pressure on the septum and occasionally by using chin straps.

Optimal pressure to be used

There is paucity of data regarding the ideal range of CPAP pressures in neonates and varying levels of initial pressures in the range of 4–8 cm of H_2O have been used. A study of infants with mild RDS showed higher end-expiratory lung volume and tidal volume, and the lowest respiratory rate and thoracoabdominal asynchrony at a pressure of 8 cm H2O compared to 0, 2, 4 and 6 cm H2O[42].

A RCT from India comparing an initial bubble CPAP of 7 cm against 5 cm of H_2O among preterm neonates (N=, 27–34 weeks) developing respiratory distress within 24 hours of birth found no statistically significant difference in the proportion of infants requiring mechanical ventilation during the first week of [(5cm H_2O: 29/133, 21.8% versus 7cm H_2O: 30/138, 21.7%), (RR of 0.99 and CI of 0.56–1.77)] [43]. There was also no difference in the in-hospital mortality, pulmonary air leaks, need of surfactant therapy, bronchopulmonary dysplasia and duration of CPAP[43]. A RCT done in the post extubation setting where neonates (*n*=93) of 23-30 week gestation with residual lung disease (needing FiO2>0.25) who were being extubated for the first time were randomized to receive low (4-6 cm) or high (7-9 cm) CPAP pressure[44]. The rates of extubation failure and re-intubation within 96 hours of extubation were significantly lower in the high CPAP pressure group. This was mainly due to strikingly lower failure rates in 500-750 g birth weight group [44]. The optimal CPAP pressure is likely to depend on the condition being treated and the leaks. Judging how much pressure is needed is still an art. If the infant shows evidence of worsening lung disease with increasing oxygen requirements, a more opaque chest X-ray, and is having chest retractions,

an increase in the pressure in increment of 1 cm H2O, up to 8 -10 cm H2O is required whereas a hyperinflated chest X-ray might necessitate decrease in CPAP.

Clinical indications for NCPAP

Post-extubation

Atelectasis and apnoea often follow extubation in preterm infants and NCPAP is used in an attempt to reduce the need to re-ventilate infants. A metanalysis of nine trials showed that infants extubated to NCPAP had a reduction in the need for additional respiratory support [RR 0.62 (0.51, 0.76); RD -0.17 (-0.23, -0.10); NNT 6[45]. However, there was no significant difference in rates of bronchopulmonary dysplasia (BPD) and there does not appear to be any harm (in terms of rates of eventual endotracheal re-intubation) from delaying treatment with NCPAP until an infant displays signs of respiratory failure, a strategy that could be used in resource poor settings.

It is to be noted that the as compared to nCPAP, synchronized nasal intermittent positive pressure ventilation (SNIPPV) decreases the frequency of post-extubation failure[40].However, both non-synchronized NIPPV as well as bi-level CPAP (BiPAP) are inconclusive as compared to CPAP in post-extubation setting and more evidence is required[40].

CPAP for respiratory distress syndrome

Randomized trials evaluating this therapy against head box oxygen were conducted mostly in the 1970's on more mature infants and used a variety of devices. Pooled analysis of these six trials[46] showed that the CPAP use reduced the risk of treatment failure (death or use of assisted ventilation) (typical risk ratio (RR) 0.65, 95% confidence interval (CI) 0.52 to 0.81; typical risk difference (RD) -0.20, 95% CI -0.29 to -0.10; number needed to treat for an additional beneficial outcome (NNTB) 5, 95% CI 4 to 10; six studies; 355 infants), lower overall mortality (typical RR 0.52, 95% CI 0.32 to 0.87; typical RD -0.15, 95% CI -0.26 to -0.04; NNTB 7, 95% CI 4 to 25; six studies; 355 infants) and lower mortality in infants with birth weight above 1500 g (typical RR 0.24, 95% CI 0.07 to 0.84; typical RD -0.28, 95% CI -0.48 to -0.08; NNTB 4, 95% CI 2.00 to 13.00; two studies; 60 infants). However the use of CDP was associated with increased risk of pneumothorax (typical RR 2.64, 95% CI 1.39 to 5.04; typical RD 0.10, 95% CI 0.04 to 0.17; number needed to treat for an additional harmful outcome (NNTH) 17, 95% CI 17.00 to 25.00; six studies; 355 infants). There was no difference in BPD,

defined as oxygen dependency at 28 days (three studies, 260 infants), as well as no difference in outcome at 9 to 14 years (one study, 37 infants).'

Even the low-cost indigenously designed CPAP systems have been shown to be effective in reducing the mortality and up-transfers among term and preterm neonates with respiratory distress in low and middle-income countries[47-48]

So in view of above advantages, CPAP became the standard of care in the management of RDS. The next question was the timing of its application in symptomatic preterm infants with RDS. Cochrane systematic review addressed this issue. There were six trials which were predominantly done in 1970s. The review concluded that the application of CPAP early in the course of the disease as compared to late CPAP was associated with a significant reduction in subsequent use of invasive ventilation (RR 0.55, NNT 6). But early CPAP had no effect on overall mortality, BPD or pneumothora.

On one hand, trials on CPAP in RDS were going on and on the other hand multiple RCTs proved the role of surfactant in preterm infants at risk for or with evidence of RDS in 1990s. Intubation, surfactant administration and mechanical ventilation became the standard of care for infants born 29 weeks' gestation[50]. Gradually with more and more understanding of the pathophysiology of RDS, it became clear that both CPAP and surfactant lead to the same final goal of establishing and maintaining functional residual capacity. People realized that surfactant administration followed by mechanical ventilation has its own disadvantages in terms of alteration in the vital parameters while intubation, trauma to airway by endotracheal tube and above all the risk of ventilation induced lung injury leading to BPD.

Delivery room (DR) CPAP and prophylactic CPAP for preterm infants

Many RCT's have addressed the question of whether NCPAP commenced soon after resuscitation, irrespective of respiratory status, reduced mortality and morbidity of very preterm infants.[51-58] IFDAS[54] trials enrolled inborn infants of 27-29 week gestation who had or were at risk of RDS and randomized them to 4 treatment groups. Group 1=early NCPAP after prophylactic surfactant; group 2=early NCPAP and selective rescue surfactant; group 3=early intermittent positive pressure ventilation (IPPV) with prophylactic surfactant; group 4=conventional management i.e. rescue IPPV and selective rescue surfactant. The requirement for mechanical ventilation within the first 5 days of life was the highest in group 3 and the lowest in group 1. There was no difference between the groups for the duration of total respiratory support (mechanical ventilation + NCPAP), oxygen dependency at 28 days

of age or 36 weeks post- conceptional age, or any neonatal morbidity. The authors concluded that the use of NCPAP following prophylactic surfactant or NCPAP alone was safe and reduced the need for mechanical ventilation when used as initial respiratory support. The REVE (REduction of VEntilation) trial was a French multicentre randomized trial aiming to demonstrate the efficacy of early NCPAP use after prophylactic surfactant administration compared to mechanical IPPV with prophylactic surfactant on the duration of mechanical ventilation[55]. Infants 25 to 27 weeks were randomized at birth when they presented with mild respiratory distress. The results were never published but have been presented. The REVE trial suggests that intubation with early surfactant administration followed by NCPAP mostly benefits 25-26 week infants.

A Cochrane meta-analysis updated in 2005 showed no difference in the rates of death, BPD, subsequent endotracheal intubation or intraventricular haemorrhage (IVH) in the prophylactic CPAP group compared with the standard treatment group[56]. This review did not include the recent trials which studied prophylactic CPAP with or without surfactant use.

The updated cochrane systematic review by Subramaniam et al included above mentioned recent trials (Table IV))[59] where prophylactic nasal CPAP was started soon after birth regardless of the respiratory status among preterm infants (under 32 weeks' gestation or <1500 grams birth weight). This was compared with the 'standard' methods of treatment such as IPPV, oxygen therapy or supportive treatment. A total of seven trials recruiting 3123 babies were included in the meta-analysis. In the comparison of CPAP with supportive care there was a reduction in failed treatment (typical RR 0.66, 95% CI 0.45 to 0.98; typical RD -0.16, 95% CI -0.34 to 0.02; 4 studies, 765 infants, very low quality evidence). There was no reduction in bronchopulmonary dysplasia (BPD) or mortality. In trials comparing CPAP with assisted ventilation with or without surfactant, CPAP resulted in a small but clinically significant reduction in the incidence of BPD at 36 weeks, (typical RR 0.89, 95% CI 0.79 to 0.99; typical RD -0.04, 95% CI -0.08 to 0.00; 3 studies, 772 infants, moderate-quality evidence); and death or BPD (typical RR 0.89, 95% CI 0.81 to 0.97; typical RD -0.05, 95% CI -0.09 to 0.01; 3 studies, 1042 infants, moderate-quality evidence). There was also a clinically important reduction in the need for mechanical ventilation (typical RR 0.50, 95% CI 0.42 to 0.59; typical RD -0.49, 95% CI -0.59 to -0.39; 2 studies, 760 infants, moderate-quality evidence); and the use of surfactant in the CPAP group (typical RR 0.54, 95% CI 0.40 to 0.73; typical RD -0.41, 95% CI -0.54 to -0.28; 3 studies, 1744 infants, moderate-quality evidence). Thus prophylactic nasal CPAP when compared to mechanical ventilation in very preterm infants reduces the need

for mechanical ventilation and surfactant and also reduces the incidence of BPD and death or BPD.

The same has been highlighted in the recommendations from American Academy of Pediatrics regarding the use of prophylactic surfactant in neonates <30 weeks gestation. There was a trend towards increased risk of BPD (RR 1.13, 95% CI 1.00-1.28) and death or BPD (RR 1.13; 95% CI 1.02-1.25) with use of prophylactic surfactant in infants born at <30 weeks gestation as compared to infants who were routinely applied CPAP in the delivery room[60].

In order to achieve the advantage of early CPAP and surfactant without the drawbacks of mechanical ventilation, few studies have compared early CPAP and prophylactic surfactant with early CPAP and rescue surfactant. The CURPAP trials[53] studied NCPAP-prophylactic surfactant and NCPAP-early rescue surfactant in infants between 25 and 28 weeks, irrespective of respiratory status. Thus, unlike the SUPPORT trial, the infants in the prophylactic surfactant group of the CURPAP trial were extubated to CPAP and not continued on mandatory mechanical ventilation. In this trial, prophylactic surfactant was not superior to NCPAP and early selective surfactant in decreasing the need for mechanical ventilation in the first 5 days of life and the incidence of main morbidities of prematurity. In VON DRM trial, on comparing the arm which received prophylactic CPAP and rescue surfactant with prophylactic CPAP and prophylactic surfactant, almost half (45% in the CPAP-rescue surfactant group and 51% in the CPAP-prophylactic surfactant group) required intubation during the first week of life like CURPAP trial. There was no difference in the primary outcome of death or CLD at 36 weeks' postmenstrual age. Other RCT's studying delivery room CPAP recruited only infants with respiratory distress. Rojas et al [61] randomized infants between 27 and 32 weeks of gestation, with respiratory distress, to NCPAP or surfactant-nCPAP soon after birth. They found that the addition of surfactant therapy to NCPAP immediately after birth reduced the need for subsequent mechanical ventilation, air-leak rates and BPD, compared with the use of NCPAP alone. A recent trial from our own country compared early routine versus late selective surfactant (need of FiO2> 0.50 beyond 2 h of life) in preterm neonates (28 to 33 weeks) with RDS on NCPAP. The results were very similar to Rojas trial. The need for mechanical ventilation in first seven days of life was significantly lower in the early surfactant group (16.2 vs. 31.6%; RR 0.41, 95% CI 0.19-0.91). The incidence of pneumothorax (1.9 vs. 2.3% and the need for supplemental oxygen at 28 days were similar in the two groups[62]

Overall, the compilation of results from all recent trials seems to suggest that NCPAP is an acceptable safer alternative to endotracheal intubation in the delivery room even in extremely premature infants and early rescue surfactant by using INSURE is a better option than prophylactic surfactant. However, it is important to note that all these trials (SUPPORT, CURPAP, COIN and VON DRM) [52-53, 57-58] have been done in extremely preterm neonates (<28 weeks) and in a setting of very high coverage by antenatal steroids (>90%). Of course, we all eagerly wait for the day when aerosolized or nebulized surfactant becomes available in the market so that the adverse effects of even short term intubation required for INSURE can be avoided.

Table IV: Studies comparing delivery room CPAP or prophylactic CPAP with conventional approach

Author	*Study design & study population*	*Comparison*	*Results*
Morley,*et al.* 2008 (COIN trial)	Multicentric RCTN=610; 25–28 +6 weeks who were spontaneously breathing in delivery room with mild to moderate respiratory distress	Delivery room CPAP (DR CPAP) vs Conventional approach*	a) No difference in composite outcome of BPD or death at 36 weeks of post conceptional age (PCA) [OR 0.80 (95% CI 0.58 –1.12)] b) DR CPAP group spent less time on mechanical ventilation (MV), surfactant need was almost half and required less postnatal steroids for BPD (P<0.05) c) Incidence of pneumothorax was high in DR CPAP group (9.1% vs 3.0%) compared to conventional group (P< 0.05)
Finer,*et al.* 2010 (SUPPORT trial)	Multicentric RCT (randomized before delivery) N=1316; 24–27 +6 weeks All neonates	Prophylactic CPAP vs Conventional approach*	a) No difference in the composite outcome of BPD or death at 36 weeks of PCA [OR 0.95 (95% CI 0.85–1.05)] b) Need of surfactant, intubation and MV, duration of MV and use of postnatal steroid for

	independent of respiratory status		BPD was less in Prophylactic CPAP group compared to conventional group ($p<0.05$) c) No statistically significant difference in air leaks
Dunn, *et al*. 2011 (VON DRM trial)	Multicentric RCT (randomized before delivery) N=648; 26–29 $^{+6}$ weeks All neonates independent of respiratory status	Prophylactic CPAP (nCPAP) *vs* Prophylactic surfactant followed by mechanical ventilation (prophylactic surfactant [PS]) = conventional approach*)vs Prophylactic surfactant with rapid extubation to CPAP (intubate -surfactant-extubate [ISX])	a) No difference in composite outcome of BPD or death in PS group at 36 weeks of post conceptional age compared to nCPAP group [OR 0.83 (95% CI 0.64–1.09)] or ISX group [OR 0.78 (95% CI 0.59–1.03)] b) In nCPAP group 48% were managed without intubation and ventilation, and 54% without surfactant treatment

**Conventional approach: Intubation, prophylactic surfactant followed by mechanical ventilation*

Table V: Studies comparing early rescue surfactant by InSurE and CPAP with CPAP Alone

Author	*Study design & study population*	*Comparison*	*Results*
Rojas, *et al*. 2009	Multicentric RCTN=279; 27–31+6 weeks who were spontaneously breathing in delivery room with evidence of respiratory distress and were on supplemental oxygen within first hour of life (15 min to 60 min)	Very early rescue surfactant by In SurE* followed by CPAPvsCPAP alone	a) Need for mechanical ventilation was significantly less in early rescue surfactant group (26% vs. 39%); [RR 0.69 (95% CI 0.49–0.97)] b) Incidence of pneumothorax was less in early rescue surfactant group (2% vs. 9%); [RR 0.25 (0.07–0.85) c) Trend toward less BPD in early rescue surfactant group (49% vs. 59%) [RR 0.84 (95% CI 0.66–1.05)]

Kandraju, *et al*. 2013	RCT N=153; 28–33+6 weeks All symptomatic neonates with RDS within first 2 hours of life	Early rescue surfactant by InSurE* followed by CPAP vs CPAP alone initially with late (FiO_2 > 0.50) selective surfactant	a) Need for mechanical ventilation was significantly less in early rescue surfactant group (16.2% vs. 31.6%); [RR 0.41 (95% CI 0.19–0.91)] b) Nosignificant difference in incidence of pneumothorax and BPD

CPAP for apnea of prematurity

CPAP is an effective method to treat apneas due to prematurity. It acts by various mechanisms-splinting the airways, stabilizing chest wall and improving oxygenation. However, there is no RCT which used current CPAP interface to support this practice. Moreover, ethically it will not be possible to compare CPAP with 'no treatment group' to treat apnea of prematurity.

Other applications (PDA, pneumonia, MAS, tracheo/bronchomalacia)

CPAP is useful in any condition which results in alveolar collapse. It relieves the signs of cardiac failure caused due to PDA in preterms. Similarly by preventing alveolar collapse, it has been used in pneumonia, transient tachypnea of newborn (TTN), postoperative respiratory management, pulmonary edema and pulmonary hemorrhage. In a retrospective cohort study comparing CPAP with Oxygen supplementation alone in 42 full term neonates with diagnosis of TTNB, there was a shorter ICU stay in the CPAP group (CPAP, 2.5±2 vs oxygen, 4.4±2.6 days; $p<0.001$). Morever, maximal oxygen fraction required was also low in CPAP group. There was no difference in the incidence of air leak or comfort level.[63] In meconium and other aspiration syndromes, application of CPAP can be beneficial by resolving the atelectatic alveoli due to alveolar injury and secondary surfactant deficiency[64]. Those cases of MAS in which chest X-ray reveals low lung volumes respond best to CPAP therapy. But one has to be extra vigilant about air leaks. In an observation cohort study of 66 infants with MAS, in whom CPAP was started at a mean age of 5.3 ± 0.7 hours, Murki et al showed that 75% could be managed successfully with CPAP alone, especially if they were inborn. The incidence of pneumothorax in their study was 2.6%[65]. There is no head to head

comparison of CPAP vs. mechanical ventilation in meconium aspiration syndrome (MAS) till date. CPAP has been used for the management of laryngo/tracheo/bronchomalacia as positive pressure distends the large airways as well and overcomes their tendency to collapse especially during expiration.

CPAP weaning

A lot of evidence has been generated on the indications and delivery of CPAP but the best strategy to wean from CPAP is still not clear. Various methods have been used to wean from nCPAP including sudden weaning of nCPAP after achieving pre-defined stability criteria, gradual decrease of nCPAP pressure and then discontinuing support (known as "pressure weaning"), repeatedly transitioning between periods on and off CPAP support, with gradual increase in the amount of time off CPAP (known as "graded-time off" or "cycling"), and weaning to high or low flow nasal cannula from nCPAP.

A survey done in 58 neonatal units in England revealed that the two-third of the units used to wean by "time off", 4% by weaning pressure and in around one-third there was no set method[66]. In Australia and New Zealand, 56% units stated that CPAP weaning was "ad hoc"[67]. Both these surveys highlights the marked variability in the practices and warrants evidence based guidance. Two systematic reviews[68-69] have been conducted so far in this direction. The cochrane review consisting three RCTs concluded that the neonates in whom CPAP pressure was weaned to a predefined level, and then CPAP was stopped completely have less total time on CPAP and shorter durations of oxygen therapy and hospital stay compared with those in whom CPAP was removed for a pre-determined number of hours each day[68]. The second review published by Amatya et al in 2015[69] included 7 RCTs. The criteria for infants' readiness ("stability criteria") to start weaning and success/failure criteria were clearly defined in all these trials. However the data could not be pooled in both the systematic reviews due to low data quality and trial heterogeneity, highlighting the need of further research. The review by Amatya et al also suggested that the optimal corrected gestational age and weight for the successful wean is 32 to 33 weeks and 1600 grams.

In a recent pilot RCT, Tang et al[70] randomized preterm infants (N=60; GA <30 weeks) to one of four groups after meeting stability criteria. Group 1: abrupt wean with HHHFNC; Group 2: abrupt wean without HHHFNC; Group 3: gradual wean with HHHFNC; Group 4: gradual wean without HHHFNC. There was no difference in the duration of respiratory support or BPD. Infants in group 1 had a significant reduction in duration of CPAP (group 1: median 1

day; group 2: 24 days; group 3: 15 days; group 4: 24 days; p = 0.002) and earlier corrected gestational age off CPAP. There was a significant difference in rate of parental withdrawal from the study, with group 2 having the highest rate. Group 3 had a significantly increased duration on HHHFNC compared to group 1.

Thus, the available evidence suggests that those born at lower gestational ages typically require a longer duration of CPAP support and abrupt stoppage of CPAP, after achieving the stability criteria seems to be the preferred approach however, the role of HHHFNC in CPAP weaning warrants further studies. Moreover, the point at which to attempt abrupt stoppage of CPAP should also be established in future trials.

Does nasal CPAP increase the risk of air leak?

Some RCT's and meta-analysis have shown that infants receiving early NCPAP have an increased risk of pneumothoraces[49, 57], a data that was contrary to earlier observational studies. An increased rate of pneumothorax may be a concern because past evidence has suggested that such an increase was associated with increased morbidity like BPD, PVL and IVH. But reassuringly, in the COIN trial, there was no significant increase in the rate of death, grade 3 and 4 intraventricular hemorrhage, peri-ventricular leukomalacia, bronchopulmonary dysplasia, or other adverse outcomes[57]. However the increased risk of air leak remains a concern and the challenge is to identify strategies which preserve the benefits of NCPAP but reduce the rate of pneumothorax. Reassuringly, the recent SUPPORT[52], CURPAP[53] and other trials did not show any increase in the incidence of air leaks. Even the trial by Tapia et al comparing CPAP / INSURE with oxygen/mechanical ventilation in spontaneously breathing VLBW weighing 800-1500g found incidence of pneumotherax to be 3.1% in the CPAP/INSURE group as compared to 5.6% in mechanical ventilation group (RR0.55 95% CT 0.16-1.82).[71] In the earlier studies, the air leaks may have been more common because of the use of much higher CPAP levels of 8 to 10 cm H2O. Such high pressures have not been used in recent trials.

Nasal trauma

This is the most common complication associated with all types of nasal prongs and nCPAP devices with a reported incidence of 20-60% across various studies[72]. Immature skin, fragile nasal septum and end-vascularisation of the columella and nostrils predispose to nasal trauma. It can range from local erythema, nasal flaring and necrosis to complete loss of nasal septum and nasal stubbing. Lower gestational age, birth weight (<32 weeks; <1500grams)

and duration of CPAP (>5days) are some of the factors which increase the frequency and severity of nasal trauma[73]. Meticulous attention should be paid to the size, position, fixation of nasal prong and ensuring that the bridge of the prong does not come in contact with the nasal septum. Adequate size of the cap, regular inspection and nasal suctioning with saline and optimizing gas humidification are some of the other measures to decrease nasal trauma. Various barrier materials like ointments and hydrocolloid dressings (tegaderm, duoderm) have been used in an attempt to mitigate contact trauma but the data is limited as of now. Recently application of silicon gel sheets on infant's nares surface has been shown to reduce the incidence (14.9% vs 4.3%; $p<0.05$) and severity of nasal injury in preterm infants on nCPAP[74].

Sepsis and CPAP

CPAP has been associated with increased incidence of nosocomial sepsis. Like any other foreign device, CPAP increases the risk of infection which is due to trauma to the nares which in turn increase the ports of entry of bacteria. CPAP support at 24 hours of age was found to be an independent predictive factor for early onset sepsis in a prospective study of 462 neonates of <28 weeks of gestation and birth weight less than 1000 grams (OR 9.8; 95% CI: 2.5-38.4)[75]

Gastric distension and CPAP

What is surprising is not that CPAP sometimes causes gaseous distension of the stomach but that it does it so rarely. This may be because, the tone in the upper and lower oesophageal sphincters is higher than the applied CPAP. It seems appropriate to use a stomach tube open to atmosphere to vent any gas. If it occurs, the "CPAP belly syndrome" is likely to be benign[76].

A recent prospective cohort study done among 27 neonates did not find any statistical significant increase in intra-gastric pressures (as measured by sensor attached to the oro-gastric tube) after 30 but within 90 minutes of the application of bubble CPAP of 6 cm of H2O as compared to baseline pressure (12.42 cm H_2O versus 12.88 cm H_2O; $p=0.834$) [77].

Recent Advances

Bilevel nasal CPAP, popularly known as BiPAP/SiPAP is a newer mode of non-invasive respiratory support similar to CPAP where two levels of CPAP (Phigh and Plow) are given at preset time intervals (T_{high} [time the CPAP pressures are high] and T_{low} [time the CPAP pressures are low]). A study evaluating BiPAP after InSurE failure to prevent the need for mechanical ventilation among VLBW neonates (n=60) found that the need of mechanical

ventilation was 27% in the historical controls as compared to 0% in the BiPAP group[78]. A RCT by Lista, *et al*. comparing BIPAP with CPAP among neonates with RDS between 28-34 weeks of gestation (*n*=40) found similar cytokine levels in serum on day 1 and 7 of life[79]. However, neonates in CPAP group required longer respiratory support and oxygen therapy, and were discharged later[79]. Another RCT comparing CPAP with BiPAP in the postextubation setting among neonates (*n*=136) with birth weight $\leq$ 1250g did not find any difference in the incidence of sustained extubation for next 7 days after extubations[80]. Thus, preliminary data is encouraging but more evidence is required in this direction before recommending BiPAP over nCPAP for the management of RDS or apnea or in post extubation setting[40].

Another recent innovation is Sea-PAP, a modification of bubble CPAP, where a segment of the expiratory tube immersed in water has been bent at an angle of 135° [81]. The rationale is to increase the amplitude of the oscillations which are superimposed on the pressure fluctuations, which may result in better recruitment of alveoli and better gas exchange. Preliminary data in animal studies are promising but the device requires clinical evaluation[82].

Long term outcomes of CPAP

In a retrospective analysis, Thomas, *et al*[83] compared the ventilator support strategy (CPAP *vs*. mechanical ventilation) at 24 h of age to predict neurodevelopmental outcomes. After adjusting for illness severity, those on CPAP at 24 hours of life had better Bayley Scores of Infant Development at 18-22 months of corrected age apart from lower BPD and lower mortality[83]. In the SUPPORT trial, there was no statistically significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months of corrected age in early CPAP group as compared to mechanical ventilation and surfactant group[84]. Further studies are required to evaluate long-term impact of CPAP on various development and respiratory outcomes.

Evidence of CPAP in low- and- middle income countries

Two recent systematic reviews[85, 86] have tried to assess the efficacy and safety of CPAP in low- and- middle income countries (LMICs) however, both reviews are limited by the paucity of studies and low quality of the available evidence highlighting the need for generating large high quality studies in these settings. Thukral et al concluded that the CPAP therapy is feasible in level 2 to 3 NICUs of LMICs. There was 66% reduction in the in-hospital mortality following CPAP therapy in preterm neonates (4 observational studies; odds ratio 0.34, 95%

confidence interval (CI) 0.14 to 0.82). However, 20 to 40% (8 observational studies) of preterm neonates failed CPAP and required mechanical ventilation. There was a very low risk of pneumothorax (0 to 7.2%) which becomes more reassuring in view of the lack of skilled manpower and sub-optimal equipments. However, high risk of nasal trauma and bleeding (up to 20%) highlights the need of good nursing care. The results of another review by Martin et al which has focused only on the bubble CPAP in LMICs also found similar results. The initial use of bubble CPAP compared with oxygen therapy reduced the need for mechanical ventilation by 30-50%. Although the mortality and the complication rates between the bubble CPAP and ventilator CPAP were similar, the CPAP failure rate was lower in the bubble CPAP group as compared to ventilator CPAP (3 RCTs, OR 0.32, 95% CI 0.16, 0.67; $P<0.003$). Better outcomes were seen in neonates with birth weight >1000 g than in neonates <1000 g, and in those with mild to moderate respiratory distress compared to neonates with more severe disease. Moreover, bubble CPAP can be effectively and safely applied by nurses and other health workers after their initial training in these settings, and thus may improve neonatal survival and quality of neonatal care[86]. Another recent retrospective cohort study from three rural hospitals of Rwanda found that bubble CPAP was feasible however, implementation remains a challenge in terms of correct identification of neonates requiring CPAP and repeated trainings and mentorship program may improve the same[87].

Most places except few referral neonatal units, teaching hospitals and medical colleges cannot provide invasive ventilation in developing countries. Therefore, CPAP appears to be the best option to manage infant with RDS and to prevent up-transfers to already over-burdened Level III/tertiary care centres. It also reduces cost of care by reducing the need for mechanical ventilation and surfactant. Early use of CPAP will be a simple and cost effective intervention in resource-limited settings. With the substantial increase in the CPAP use over last decade, future seems promising. However, dependence on imported CPAP devices, lack of an ideal interface, non-availability of round-the-clock air/oxygen supply, surfactant and backup ventilation, lack of awareness and expertise among doctors and inadequately trained nursing staff are the major challenges. This situation is further compounded by overcrowded delivery rooms and lack of NICU beds. Good antenatal care including high antenatal steroid coverage, timely referral, and optimum delivery and newborn care practices should be equally addressed to get maximum benefits from CPAP.

Conclusions

Nasal CPAP is an effective, safer and preferred mode of primary respiratory support for preterm newborns of all sizes. It is also useful following extubation from mechanical ventilation, for apnea of prematurity and a host of other causes of respiratory distress in the newborn. In fact, early CPAP in preterm infants with respiratory distress also reduces the need for surfactant therapy. Short bi-nasal prongs are the best interface currently. However, no significant and consistent differences in clinical outcomes have been demonstrated between different methods of CPAP generators.

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