

## Continuous Positive Airway Pressure in Preterm Neonates: An Update of Current Evidence and Implications for Developing Countries

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**Context:** Continuous Positive Airway Pressure (CPAP) is a cost-effective and minimal invasive respiratory support for the newborn.

**Objective:** To review the evidence related to various aspects of CPAP usage and its applicability for developing countries.

**Evidence Acquisition:** We conducted a literature search on PubMed, CENTRAL, and Cochrane Database of Systematic Reviews using the terms 'CPAP' OR 'continuous positive airway pressure' OR, non-invasive ventilation' AND 'newborn' OR 'neonate' OR 'infant'. We also searched the reference lists from the above articles and of review articles. Extracted manuscripts and reviews were analyzed and results related to various aspects of CPAP usage were summarized in narrative form.

**Results:** Early use of CPAP with early rescue surfactant (InSurE) is the ideal approach for management of respiratory distress syndrome in preterm and extremely preterm infants. Delivery room CPAP is feasible and reduces the need for surfactant and mechanical ventilation by nearly 50%. Prophylactic surfactant for extreme preterms should be discouraged. Heated humidified high flow nasal cannula is best utilized for post-extubation respiratory support. The search for ideal interface still continues and binasal prongs or nasal masks are the good contenders. Evidence on the ideal CPAP delivery is still inconclusive.

**Conclusions:** CPAP, if used early and judiciously, is an effective intervention and need immediate scaling-up in resource-limited settings. Future research should focus on the ideal interface and the CPAP delivery methods.

**Keywords:** *Continuous positive airway pressure, Mechanical ventilation, Noninvasive ventilation, Neonate.*

Continuous Positive Airway Pressure (CPAP) is a well-established mode of respiratory support in preterm newborns. Advancement in technology, increasing survival of extremely preterm newborns and better understanding of various respiratory diseases led to new evidence in this field over last decade. It is important to update ourselves on the recent changes in the practice of CPAP and its implications for resource-limited settings.

We reviewed evidence for the clinical use of CPAP as a primary treatment for respiratory distress syndrome (RDS), delivery room CPAP, CPAP generator, heated humidified high flow nasal cannula (HHHFNC) and CPAP interface in neonates.

### EVIDENCE ON CLINICAL USE

#### Primary Treatment of RDS

*CPAP vs no CPAP (Hood oxygen):* Meta-analysis evaluating CPAP against head box oxygen showed that CPAP use reduced the overall rate of mortality [RR 0.52 (95% CI 0.32, 0.87)] and the rate of the combined outcome of death or assisted ventilation [RR 0.70 (95% CI 0.55, 0.88)]. However, there was increased risk of

pneumothorax [RR 2.64 (95% CI 1.39, 5.04); NNH 17 (17, 25)][1]. Use of CPAP has also shown to decrease the need for up-transfers to higher centers [2]. The introduction of CPAP in a level II special newborn care unit significantly reduced the need for up-transfers as compared to pre-CPAP epoch, especially in very low birth weight (VLBW) and preterm infants [3].

*Early vs late CPAP:* The application of CPAP early in the course of the disease before alveolar collapse occurs may work better than late CPAP by reducing lung damage and promoting lung function and surfactant pool. In the systematic review that compared early CPAP (starting CPAP at the time of randomization) vs. late CPAP (initiating late in the course of disease when FiO<sub>2</sub> requirement is > 0.60), early CPAP was associated with a significant reduction in subsequent use of mechanical ventilation [RR 0.55, (95% CI 0.32, 0.96); NNT 6]. But early CPAP had no effect on overall mortality, bronchopulmonary dysplasia (BPD) or pneumothorax [4].

*Delivery room/very early CPAP:* The conventional approach of managing extreme premature infants was intubation, surfactant administration and mechanical

ventilation. Gradually it was realized that both CPAP and surfactant lead to the same final goal of establishing functional residual capacity. Recently CPAP has been used to stabilize neonates immediately after resuscitation in the delivery room. Three high-quality randomized controlled trials compared delivery room CPAP (DR CPAP or prophylactic CPAP) with conventional approach [5-7] (**Table I**). When used early in the delivery room in extreme preterm infants (gestation <28 weeks), either prophylactic [6,7] or early rescue [5], CPAP was associated with almost 50% reduction in need for intubation mechanical ventilation, and surfactant usage in

comparison to 'mechanical ventilation with or without surfactant'. The risk of death or BPD at 36 weeks was comparable between the two treatment approaches in these trials. Thus it is clear that initial stabilization on CPAP and provision of rescue surfactant should be the preferred approach among preterm neonates  $\leq 28$  weeks of gestation.

*CPAP and surfactant (InSurE strategy):* CPAP and surfactant work together towards establishing and maintaining functional residual capacity in RDS. Verder, *et al.* [9] described a technique, InSurE (Intubation,

**TABLE I:** STUDIES COMPARING DELIVERY ROOM CPAP OR PROPHYLACTIC CPAP WITH CONVENTIONAL APPROACH

Author	Study design and population	Comparison	Results
Morley, <i>et al.</i> , 2008 (COIN trial)	Multicentric RCT (N=610); 25-28 <sup>+6</sup> weeks who were spontaneously breathing in delivery room with mild to moderate respiratory distress.	Delivery room CPAP (DR CPAP) vs Conventional approach*	<ul style="list-style-type: none"> <li>a) No difference in composite outcome of BPD or death at 36 weeks of post conceptual age (PCA) [OR 0.80 (95% CI 0.58-1.12)]</li> <li>b) DR CPAP group spent less time on mechanical ventilation (MV), surfactant need was almost half and required less postnatal steroids for BPD (P&lt;0.05)</li> <li>c) Incidence of pneumothorax was high in DR CPAP group (9.1% vs 3.0%) compared to conventional group (P&lt;0.05)</li> </ul>
Finer, <i>et al.</i> , 2010 (SUPPORT trial)	Multicentric RCT (randomized before delivery) N=1316; 24-27 <sup>+6</sup> weeks All neonates independent of respiratory status	Prophylactic CPAP vs Conventional approach*	<ul style="list-style-type: none"> <li>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)]</li> <li>b) Need of surfactant, intubation and MV, duration of MV and use of postnatal steroid for BPD was less in Prophylactic CPAP group compared to conventional group (p&lt;0.05)</li> <li>c) No statistically significant difference in air leaks</li> </ul>
Dunn, <i>et al.</i> , 2011 (VON DRM trial)	Multicentric RCT (randomized before delivery) N=648; 26-29 <sup>+6</sup> 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])	<ul style="list-style-type: none"> <li>a) No difference in composite outcome of BPD or death in PS group at 36 weeks of post conceptual 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)]</li> <li>b) In nCPAP group 48% were managed without intubation and ventilation, and 54% without surfactant treatment</li> </ul>

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

surfactant, extubation), of administering surfactant to symptomatic preterm neonates who were stabilized on CPAP. Meta-analysis of six trials comparing early surfactant administration with brief mechanical ventilation (1 hour) followed by extubation *vs* later selective surfactant and continued mechanical ventilation in neonates with RDS reported that earlier strategy is associated with a significant reduction in need of mechanical ventilation (RR 0.67, 95% CI 0.57-0.79) and BPD (RR 0.51, 95% CI 0.26-0.99), but the relative contribution of early surfactant in decreasing the incidence of BPD remains speculative [9].

Verder, *et al.* [10] and Reininger, *et al.* [11] showed that CPAP along with surfactant (by InSurE) as compared to CPAP alone in symptomatic preterm neonates with RD decreases the need of mechanical ventilation. The CURPAP trial [12] and the VON DRM trial [7] reported that prophylactic surfactant was not superior to nasal CPAP and early rescue surfactant in decreasing the need for mechanical ventilation in the first few days of life. Moreover, there was no difference in death or BPD at 36 weeks' postmenstrual age. A recent Cochrane systematic review (that included the SUPPORT and VON DRM trials) of prophylactic *vs* selective use of surfactant concluded that the benefits of prophylactic surfactant in terms of decreased air leaks and decrease mortality no longer holds true in contrast to the results of previous

meta-analysis, which included studies when prophylactic or DR CPAP application was not practiced and the rate of coverage of antenatal steroids was low [13]. Moreover, a meta-analysis of these two studies alone demonstrated a compelling trend toward an increase in the risk of neonatal mortality or BPD associated with the use prophylactic surfactant when compared with early stabilization on CPAP with selective use of surfactant (typical RR 1.12, 95% CI 1.02, 1.24) [13]. The same has been highlighted in the recent 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 [14].

Two trials studied the ideal timing of rescue surfactant administration in moderately preterm infants (27 to 33 weeks of gestation) supported with CPAP within the first 1-2 hours of life. In both these trials for infants with RDS on CPAP, early addition of surfactant in comparison to CPAP alone was associated with lesser need for subsequent mechanical ventilation (**Table II**) [15,16].

Overall, the current evidence supports CPAP as an acceptable safer alternative to endotracheal intubation in

**TABLE II** STUDIES COMPARING EARLY RESCUE SURFACTANT BY INSURE AND CPAP WITH CPAP ALONE

Author	Study design and population	Comparison	Results
Rojas, <i>et al.</i> , 2009	Multicentric RCT (N=279); 27-31 <sup>+6</sup> 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 InSurE* followed by CPAP <i>vs</i> CPAP alone	a) Need for mechanical ventilation was significantly less in early rescue surfactant group (26% <i>vs.</i> 39%); [RR 0.69 (95% CI 0.49-0.97)] b) Incidence of pneumothorax was less in early rescue surfactant group (2% <i>vs.</i> 9%); [RR 0.25 (0.07-0.85)] c) Trend toward less BPD in early rescue surfactant group (49% <i>vs.</i> 59%) [RR 0.84 (95% CI 0.66-1.05)]
Kandraju, <i>et al.</i> , 2013	RCT (N=153); 28-33 <sup>+6</sup> weeks All symptomatic neonates with RDS within first 2 hours of life	Early rescue surfactant by InSurE* followed by CPAP <i>vs</i> CPAP alone initially with late (FiO <sub>2</sub> >0.50) selective surfactant	a) Need for mechanical ventilation was significantly less in early rescue surfactant group (16.2% <i>vs.</i> 31.6%); [RR 0.41 (95% CI 0.19-0.91)] b) No significant difference in incidence of pneumothorax and BPD

\*InSurE- Intubation, surfactant, extubation.

the delivery room, and to early rescue surfactant (InSurE) for preterm infants with RDS. However, it is important to note that all these recent trials (COIN, SUPPORT, VON DRM and CURPAP) have been done in extremely preterm neonates (<28 weeks) where the use of antenatal steroid coverage was very high (>90%).

### Post-extubation

Atelectasis and apnea often follow extubation in preterm neonates and nasal CPAP is used in an attempt to reduce the need for re-ventilation. A meta-analysis of nine trials showed that neonates extubated to CPAP as compared to head box oxygen had less incidence of respiratory failure (apnea, respiratory acidosis and increased oxygen requirements) [17].

### Apnea of Prematurity

There is widespread use of CPAP along with methylxanthines in treatment of apnea of prematurity. However, there is no RCT which used current CPAP interface to support this practice. Moreover, ethically it may not be possible to compare CPAP with 'no treatment group' to treat apnea of prematurity.

### Other Applications

CPAP may be useful in other conditions that result in

alveolar collapse or airway narrowing. It relieves the signs of cardiac failure due to patent ductus arteriosus. Similarly, it is often used in the management of pneumonia, transient tachypnea of newborn, postoperative respiratory management, pulmonary edema and pulmonary hemorrhage. In meconium aspiration syndromes (MAS), application of CPAP can be beneficial by resolving the atelectatic alveoli due to alveolar injury and secondary surfactant deficiency [18]. In an observational study of 66 neonates with MAS, in whom CPAP was started at a mean age of 5.3 hours, Murki, *et al.* [19] showed that 75% could be managed successfully with CPAP alone, especially if they were inborn. Incidence of pneumothorax in this study was 2.6% [19]. There is no head-to-head comparison of CPAP with mechanical ventilation in MAS. CPAP has been used for the management of laryngo/tracheo/bronchomalacia as positive pressure distends the large airways as well, and overcome their tendency to collapse, especially during expiration.

### Appropriate Pressure for CPAP

There is paucity of data regarding the ideal range of CPAP pressures in neonates [20]. In a recent RCT, neonates ( $n=93$ ) of 23-30 week gestation with residual lung disease (needing  $FiO_2 > 0.25$ ) who were being

**TABLE III** RECENT TRIALS OF CPAP WEANING

Author	Study design and population	Comparison	Results
Abdel-Hady, <i>et al.</i> , 2011	RCT ( $N=60$ ); $\geq 28$ weeks who were clinically stable on NCPAP of 5 cmH <sub>2</sub> O with $FiO_2 < 0.30$ for at least 24 hours	No nasal cannula (No-NC) group: Infants kept on NCPAP until they were on $FiO_2=0.21$ for 24 h, and then were weaned off NCPAP completely without any exposure to NC vs Nasal cannula (NC) group: Infants weaned off NCPAP when $FiO_2$ was $\leq 0.30$ to NC (2 L/min of oxygen) followed by gradual weaning from oxygen	a) No-NC group had fewer days on oxygen and shorter duration of respiratory support  b) No difference regarding success of weaning from NCPAP
Todd, <i>et al.</i> , 2012	Multicentric RCT ( $N=177$ ); <30 weeks who were clinically stable on CPAP 4-6 cm with $FiO_2 < 25\%$ for at least 12 hours	M1: Taken 'OFF' CPAP with the view to stay 'OFF' vs M2: Cycled on and off CPAP with incremental time 'OFF' vs M3: As with M2, cycled on and off CPAP but during 'OFF' periods were supported by nasal cannula at a flow of 0.5 l/min	Method 1 significantly shortened CPAP weaning time, CPAP duration, oxygen duration, BPD and length of admission
O'Donnell, <i>et al.</i> , 2013	2 center RCT ( $N=78$ ); VLBW infants who were stable on CPAP of 3-5 cm H <sub>2</sub> O with $FiO_2=0.21$ for 24 hours	Nasal prong group: Treated with low-flow (1.0 L/min) nasal prongs with room air vs Spontaneous breathing in room air	No significant difference in failure rate of weaning from CPAP [41% in nasal prong group vs 31% in spontaneous breathing group ( $P=0.48$ )].

extubated for the first time were randomized to receive low (4-6 cm) or high (7-9 cm) CPAP pressure [21]. 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 [21].

### Weaning

A questionnaire survey done in 58 units in England revealed that 36 (66%) of the units used to wean by 'time off', 2 (4%) by weaning pressure, and in remaining 30%, there was no set method [22]. A randomized trial comparing the strategy of weaning pressure with one of increasing time off-CPAP showed a significant shorter duration of weaning with the 'pressure' strategy (1.5 days in pressure group vs 9 days in 'time off';  $P$  0.001) [23]. A Cochrane review of three RCTs concluded that neonates in whom CPAP pressure was weaned to a pre-defined 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 [24]. The overall evidence (**Table III**) [25-27] favors abrupt stoppage of CPAP after achieving the stability criteria without any exposure to nasal cannula. The point at which to attempt abrupt stoppage of CPAP needs to be established in future trials.

### IDEAL CPAP DEVICE

#### CPAP Pressure Generator (**Table IV**) [28-33]

Bubble CPAP has the advantage over ventilator CPAP in producing pressure oscillations superimposed over the pressure fluctuations, as a result of spontaneous breathing. The noisy pressure waveform superimposed over pressure fluctuations (stochastic resonance effect) promotes lung recruitment resulting in better oxygenation [29]. Moreover, additional benefits accrue with bubble CPAP due to higher delivered pressure as compared to set pressure because of its flow-dependent nature. In spite of theoretical advantage of variable flow CPAP devices, data supporting its clinical superiority across all the settings are scarce (**Web Table I**) [34-48]. In a recent RCT comparing Benveniste valve (Jet CPAP) with bubble CPAP in neonates with RDS, there was no difference in the failure rate, mortality or any other morbidity between the two groups. The prong displacements were more common with Benveniste valve (Jet CPAP) as compared to bubble CPAP. However, the pain scores in neonates were lesser with Benveniste valve [49].

Though, there is some evidence for the superiority of IFD and bubble CPAP over ventilator CPAP but the differences in study design, indications, short study

**TABLE IV:** STUDIES COMPARING BUBBLE CPAP AND VENTILATOR CPAP

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

epochs and insufficient relevant clinical outcomes necessitate the need for further studies on this issue.

### Heated Humidified High-flow Nasal Cannula (HHFNC)

Simple nasal cannulas with an outer diameter of 3 mm and flows up to 2 L/min, have been reported to deliver CPAP. In humidified high-flow nasal cannula (HHFNC), warm and humidified respiratory gases are delivered at flow rates between 2 to 8 L/min. A systematic review of 19 studies concluded that HHHFNC may be as effective as nasal NCPAP in improving respiratory parameters, but its efficacy and safety in preterm neonates need further research [50]. A recent multicentric RCT in 432 neonate (28 to 42 weeks) comparing HHHFNC with CPAP device for planned nasal CPAP support, as either primary therapy or in post-extubation setting did not find any difference in early failure (10.8% vs 8.2%) or subsequent need for any intubation (15.1% vs 11.4%). HHHFNC neonates remained on the study mode significantly longer than nasal CPAP neonates (median: 4 vs 2 days,  $P < 0.01$ ), but there were no differences for days on supplemental oxygen, and BPD [51]. Another RCT on 132 neonates (<32 weeks gestation) in post-extubation setting did not find any difference in extubation failure rate (22% in HHHFNC vs 34% in NCPAP) within seven days after extubation. However, the nasal trauma score was significantly less in HHHFNC group (3.1 vs 11.8;  $P < 0.001$ ) as compared to NCPAP group [52]. A randomized crossover trial found similar patient comfort score in preterm infants ( $n = 20$ , <34 weeks gestation) who were treated with HHHFNC or NCPAP due to mild respiratory illness. However, parents preferred HHHFNC because of better child satisfaction, interaction and possibility to take part in care [53]. In a recent multicentric non-inferiority RCT done among neonates <32 weeks gestation ( $n = 303$ ) in post-extubation setting, the use of HHHFNC was not inferior to NCPAP. The treatment failure within seven days after extubation occurred in 34.2% in HHHFNC group as compared to 25.8% in NCPAP group [54]. However, like previous trials, neonates in HHHFNC group had a significantly lower incidence of nasal trauma than those in the NCPAP group (39.5% vs 54.3%,  $P = 0.01$ ). Thus, HHHFNC may have a potential role as an alternative to CPAP in post-extubation setting due to its ease of application and less nasal trauma.

### Patient Interface

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 prong which is actually a nasopharyngeal prong

has the disadvantages of a 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, F and P, 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 [55]. In patients with RDS, short binasal prongs were found to be superior to nasopharyngeal prongs in terms of lower oxygen requirement and less respiratory rate in first 48 hours [56]. Information about short binasal prongs is limited. 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 in the nostrils of active patients and nasal hyperemia occurs more frequently with its use [57].

In another RCT among VLBW neonates, comparing nasal prongs with nasal mask, no significant difference was noted in the incidence of nasal injury [58]. A 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%;  $P = 0.007$ ) [59]. In a recent RCT from India, Chandrasekaran, *et al.* [60] 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%,  $P < 0.01$ ) [60]. 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 [61]. Nzegwu, *et al.* [62], 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  $FiO_2 \leq 0.35$  [62].

### 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 ( $P_{high}$  and  $P_{low}$ ) 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 [63]. ARCT by Lista, *et al.* [64] 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. However, neonates in CPAP group required longer respiratory support and oxygen therapy, and were discharged later [64]. Another RCT comparing CPAP with BiPAP in the post-extubation setting among neonates ( $n=136$ ) with birth weight  $\leq 1250$ g did not find any difference in the incidence of sustained extubation for next 7 days after extubation [65]. Thus, preliminary data is encouraging but more evidence is required in this direction.

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  $135^\circ$  [66]. 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 [67].

#### LONG TERM OUTCOMES OF CPAP

In a retrospective analysis, Thomas, *et al.* [68] 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 [68]. 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 [69]. Further studies are required to evaluate long-term impact of CPAP on various development and respiratory outcomes.

#### IMPLICATIONS AND APPLICABILITY

Assuming the incidence of RDS to be 1.2% among live-births, nearly 1,86,000 infants each year are affected with RDS in India [70]. With a reported mortality of 57% to 89% among infants with RDS, nearly 100,000 infants each year are estimated to die due to RDS [71]. Mechanical ventilation and CPAP are the mainstay in the management of RDS. 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 [72-74].

A recent systematic review [75] examining the efficacy and safety of bubble CPAP in neonates with respiratory distress in low- and middle-income countries found that 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 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 [75].

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 centers. It also reduces cost of care by reducing the need for mechanical ventilation and surfactant [76]. 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, timely referral, and optimum delivery and newborn care practices should be equally addressed to get maximum benefits from CPAP.

Our initial focus should be primarily on infants with gestation  $>28$  weeks to make a larger impact. However, as survival of extremely low birth weight neonates has improved, tertiary care centers should focus on very early CPAP in the delivery room. The concerns of associated morbidities and long-term sequelae should be addressed with simultaneous improvements in effective resuscitation, asepsis, breast milk feeding, aggressive nutrition, intensive monitoring, and screening for complications.

CPAP is a big boon for resource-limited countries, provided it is started early and used judiciously along with holistic care and proper follow-up services.

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