

Delivery room CPAP in improving outcomes of preterm neonates in low-and middle-income countries: A Systematic review and network meta-analysis

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Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding Sources: None

Word count: 3071

Figures: 5

Tables: 1

ABSTRACT

Aim: To study the effectiveness of delivery room continuous positive airway pressure (DRCPAP) and its impact on outcomes of preterm neonates in LMICs. DRCPAP was compared with four interventions: oxygen supplementation, late DRCPAP, sustained lung inflation with DRCPAP and surfactant therapy along with DRCPAP.

Methods: Medline, Embase, CENTRAL, Web of science and CINAHL were searched. Observational studies and randomized controlled trials (RCT) from LMICs were included. Data from observational studies were synthesized in a meta-analysis and from RCTs in a Bayesian random effects network meta-analysis (NMA). Requirement of invasive mechanical ventilation was the primary outcome measure.

Results: Of the 18 studies included, data from 11 studies (4 observational studies, 7 RCTs) enrolling 4210 preterm neonates were synthesized. Very low certainty of evidence (CoE) from observational studies indicated a trend towards decreased risk of need for invasive ventilation with DRCPAP when compared to oxygen supplementation [RR 95%CI: 0.75 (0.56-1.00)]. Moderate CoE from NMA of RCTs showed a trend towards lesser surfactant administration with DRCPAP compared to oxygen supplementation [RR 95% CrI: 0.69 (0.44, 1.06)]. None of the interventions decreased the risk of combined outcome of mortality or BPD at 36 weeks' PMA.

Conclusions: For preterm infants born in LMICs, DRCPAP might be associated with decreased requirement of invasive ventilation and surfactant but may not translate to reduced mortality or BPD. Future multi-center observational studies from LMICs with robust study methodology evaluating the major barriers of introducing DRCPAP and its impact on important clinical outcomes in preterm neonates are needed.

Key words: Delivery room CPAP, prematurity, preterm, neonates

1. INTRODUCTION

Prematurity is a leading cause of neonatal mortality worldwide.^{1,2} Recognizing that over 80% of preterm births occur in the impoverished regions of Asia and sub-Saharan Africa,² the World Health Organization's Every Newborn Action Plan (ENAP) mandates improving the care practices of preterm neonates in low-and middle-income countries (LMICs).³ The ENAP set out the goal of achieving neonatal mortality rates (NMR) of less than 10 per 1000 live births by the year 2035.

The generalizability of evidence-based care practices stemming from high income countries (HICs) to low resource settings is often marred by obstacles ranging from the general dearth of resources to scarcity of trained health care personnel.^{4,5} Some of the delivery room interventions that have been systematically evaluated to be effective in improving the outcomes of preterm neonates in LMICs include training personnel on resuscitation, preventing infections through clean practices and maintaining normothermia.⁶⁻⁹ Evidence from large multi-centric randomized controlled trials (RCTs) conducted in HICs indicate that initiation of delivery room Continuous Positive Airway Pressure (DRCPAP) in preterm neonates with labored breathing is effective in decreasing the need for invasive mechanical ventilation, requirement of surfactant and the combined outcome of death or bronchopulmonary dysplasia (BPD).¹⁰⁻¹³ Based on a moderate certainty of evidence (CoE) from the meta-analysis of these trials, the neonatal task force of International Liaison Committee of Resuscitation (ILCOR) (2020) continued with its previous global 'conditional recommendation' for initiating DRCPAP in preterm neonates with respiratory distress.¹⁴

A recent systematic review concluded that CPAP use in the NICU in LMICs is safe and can improve the outcomes of preterm neonates.¹⁵ Consequently, some guideline generating bodies from LMICs do recommend initiating CPAP in the DR for preterm neonates with respiratory

distress.¹⁶ However, this raises several questions. Most of the aforementioned RCTs from HICs evaluating DRCPAP had compared its relative efficacy with the use of prophylactic surfactant with or without invasive ventilation, whose use is a rarity in the delivery rooms in LMICs where provision of oxygen is the most frequent, and often the only, available intervention.¹⁰⁻¹³ Also, recent evidence suggest that DRCPAP use might be associated with an increased risk of pneumothorax, even in high resource settings with appropriate training of personnel and monitoring.¹⁷ Further, the feasibility of initiating DRCPAP in LMICs might be compromised due to lack of equipment such as blenders, T-piece resuscitators or compressed sources of oxygen and air.¹⁸ Finally, ensuring continued CPAP application initiated in the delivery room during the transport of the neonate to the NICU is a daunting task in LMICs due to additional bottlenecks especially absence of a well-equipped transport system.¹⁸ Hence, this systematic review and meta-analysis was performed to study the barriers and feasibility of introducing DRCPAP in LMICs. We also aimed to evaluate the impact of a policy change from the traditional strategies of oxygen supplementation or endo-tracheal positive pressure ventilation (PPV) for preterm neonates with signs of respiratory distress at birth to an early provision of DRCPAP in LMICs.

2. METHODOLOGY

The protocol was registered with PROSPERO (CRD42021241101).¹⁹ The reporting of this review is in accordance with PRISMA framework.²⁰

2.1. Literature search

Five databases, Medline, Embase, CENTRAL, Web of science and CINAHL were searched from inception until 19th February 2021. The search strategy is given in **Supplement Table 1**. Conference abstracts were excluded. Both English and non-English literature was eligible for inclusion. Observational studies and RCTs were included. Two authors independently searched the literature.

2.2. Inclusion criteria

Studies from LMICs (World Bank country classifications 2020)²¹ that had included preterm neonates born at less than 37 weeks' gestation and evaluated DRCPAP were eligible for inclusion. The comparator arms of our systematic review included adjunctive practices such as sustained lung inflation (SLI) prior to DRCPAP initiation, use of surfactant replacement therapy in the delivery room in addition to DRCPAP, oxygen supplementation through low flow prongs or hood and invasive ventilation.

2.3. Outcomes

The primary outcome was requirement of invasive mechanical ventilation any time after admission to NICU. The secondary outcomes included requirement of surfactant therapy, pneumothorax, BPD at 28 days of postnatal life and at 36 weeks' postmenstrual age (PMA), intraventricular hemorrhage (IVH) \geq grade 2 (as per Papile's classification)²², mortality or BPD at 36 weeks' PMA and mortality before discharge. The major barriers in introducing DRCPAP in LMICs and the proportion of eligible preterm neonates who were started on DRCPAP after a policy change was also studied.

2.4. Data Extraction and synthesis

Data were extracted by two authors independently. Observational studies on DRCPAP with a comparator arm were synthesized using random effects meta-analysis. Statistical heterogeneity was evaluated using Cochran Q, I^2 and τ^2 values. The effect estimates for the various outcomes were expressed as risk ratio (RR) with 95% confidence interval (CI). RCTs were evaluated using a network meta-analysis (NMA) using a Bayesian random effects approach with non-informative priors. Generalized linear models with four chains, burn-in of 50,000 iterations, 1,00,000 iterations and 10,000 adaptations were used. Network plots were used to evaluate network connectivity. Gelman-Rubin plots, trace and density plots were assessed for model

convergence. Node-splitting was attempted to detect inconsistency between the direct and indirect fraction of evidence. Final estimates were reported as risk ratios (RR) [95% credible intervals (CrI)]. Interventions were ranked according to their efficacy using the surface under the cumulative ranking curve (SUCRA) plots.²³

2.5. Risk of bias (RoB) and Certainty of evidence (CoE)

The RoB in observational studies without a comparator arm was done using a modified QUIPS scale, in observational studies with a comparator arm using the ROBINS-I tool and in RCTs using Cochrane RoB tool 2.0.²⁴⁻²⁶ Two authors evaluated the risk of bias independently. CoE was done using the GRADE working group recommendations for all the outcomes.^{27,28}

3. RESULTS

Of the 1331 articles that were screened after removal of duplicates, full texts of 306 studies were evaluated. A total of 18 studies were included in the systematic review. These comprised of observational studies without a comparator arm: six studies²⁹⁻³⁴, observational studies with a comparator arm: five studies³⁵⁻³⁹ and RCTs: seven studies⁴⁰⁻⁴⁶. Eleven (4210 neonates) out of the eighteen studies were synthesized in a meta-analysis.^{35-38,40-46} The literature search process is given in **Figure 1**.

3.1. Characteristics of included studies

The included studies were from Brazil, Egypt, India, Iran, Malaysia, Nigeria, South Africa, Turkey, Ukraine and South American neonatal network. The predominant population evaluated were very low birth weight (VLBW) neonates or those born at less than 32 weeks' gestation. The characteristics of included studies is given in **Table 1**.

3.1.1. DRCPAP care practices

DRCPAP was initiated prophylactically in preterm neonates in five studies^{33,34,39,40,46} and as a rescue therapy in preterm neonates with varying severity of respiratory distress in eight studies.^{29,35,36,38,41,42,44,45}. The various comparator arms evaluated by the included studies were:

oxygen supplementation, DRCPAP with early INSURE (Intubate SURfactant and Extubate), delayed initiation of DRCPAP after 30 minutes of life, SLI with DRCPAP and surfactant administration followed by invasive mechanical ventilation.

The type of CPAP devices used varied across the studies with seven studies using a T-piece resuscitator^{29,34,40,42-44,46}, four using bubble CPAP^{30,33,35,45} and three ventilator CPAP.^{36,38,41} Nine of the 18 included studies had used blended oxygen while instituting CPAP therapy.^{32,33,34,36,37,38,42,45,46} While eight studies had used a relatively lower fraction of inspired oxygen (FiO₂) threshold of 0.3 – 0.4 for surfactant administration^{29,32,33,34,36,38,42,46}, two studies had used a threshold of ≥ 0.6 ^{41,45} and one study had used only clinical respiratory distress score as a guide for surfactant administration.³⁰

3.1.2. Implementing a policy change to DRCPAP and associated barriers in LMICs

Boo et al. in their multi-center study from Malaysia reported that only 28.4% (IQR 14.3%-38.7%) of the healthcare facilities used DRCPAP despite a policy change adopted by the hospitals in the network.³⁷ Non-availability of compressed sources of air and oxygen was reported as the most commonly encountered barrier by 44.1% of the hospitals. Similarly, Viera et al. indicated that only 54% of the eligible very preterm neonates received DRCPAP, while 36% were intubated and 10% received oxygen supplementation.³⁶ On the contrary, Abelenda et al. had showed that after a practice change to using DRCPAP in very preterm VLBW neonates, 95% of the eligible neonates could be stabilized on DRCPAP and transported to the NICU using a CPAP equipped incubator.³⁵

3.2. Qualitative review of observational studies without a comparator arm

Afjeh et al. reported that any form of escalation of therapy to higher forms of respiratory support was required in 33.9% of the VLBW neonates started on DRCPAP and in 68.3% of the VLBW neonates who were started on oxygen supplementation.²⁹ This was despite the oxygen supplementation arm having lesser respiratory distress score compared to DRCPAP

group. Ajanwaenyi et al. showed the synergistic benefits of minimally invasive surfactant therapy (MIST) used in conjunction with DRCPAP for the outcome of mortality in extremely low birth weight (ELBW) and VLBW neonates.³⁰ Quite similarly, Dobryanskyy et al. had shown that in neonates who were stabilized with DRCPAP, those who were given early surfactant at a lower FiO₂ threshold had lower risk of needing invasive ventilation in the first five days of life, when compared to those who were given surfactant late only when they required invasive ventilation.³²

The studies by Goncalves-Ferri et al. and Atalay et al. showed that a very high proportion of ELBW neonates (85.7-100%) eventually required intubation in the delivery room or NICU, despite the use of DRCPAP.^{31,33} On the contrary, Kirsten et al. indicated that 68.5% of neonates were successfully managed on DRCPAP without any use of surfactant.³⁴

3.3. Meta-analysis of observational studies with a comparator arm and Network meta-analysis of RCTs

3.3.1. Requirement of invasive mechanical ventilation

Meta-analysis of observational studies showed that there was a trend towards decreased invasive ventilation amongst neonates in the DRCPAP group when compared to those who received oxygen supplementation [RR 95% CrI: 0.75 (0.56-1.00)]. (**Figure 2A**) NMA of RCTs did not show any statistical significance between these two interventions [RR 95% CrI: 0.79 (0.47-1.33)]. The results of NMA are depicted in **Figures 3-5**. The network characteristics is given in **Supplement Table 2**.

3.3.2. Need for surfactant replacement

Pooled estimate from observational studies indicated that there was a trend towards lesser requirement of surfactant in the DRCPAP group when compared to those who received oxygen supplementation [RR 95% CI: 0.85 (0.72-1.00)]. (**Figure 2B**) A similar trend favoring

DRCPAP over oxygen supplementation was observed in the NMA of RCTs [RR 95% CrI: 0.69 (0.44-1.06)]. (**Supplement Figure 1 – 3**)

3.3.3. *Pneumothorax*

Meta-analysis of observational studies revealed that there was no statistically significant difference in the risk of pneumothorax between the two groups [RR 95% CI: 0.95 (0.58-1.56)]. (**Supplement Figure 4A**)

3.3.4. *BPD*

No difference in the risk of BPD at 28 days between DRCPAP and no DRCPAP group was observed as reported by one observational study [RR 95% CI: 0.89 (0.53-1.49)] (**Supplement Figure 4B**) or from the pooled network estimate of RCTs [RR 95% CrI: 0.68 (0.29-1.38)] (**Supplement Figures 5-7**). One observational study reported a decreased risk of BPD at 36 weeks' PMA in DRCPAP group when compared to those who were not stabilized on DRCPAP [RR 95% CI: 0.69 (0.53-0.88)]. (**Supplement Figure 4C**) No such difference was found in the network estimates of RCTs. (**Supplement Figures 8-10**)

3.3.5. *BPD or mortality at 36 weeks' PMA*

Meta-analysis of observational studies showed that the risk of the combined outcome of BPD or mortality at 36 weeks' PMA was reduced in the DRCPAP group when compared to no DRCPAP group [RR 95% CI: 0.57 (0.49-0.66)]. (**Figure 2C**) Analysis of RCTs did not reveal any difference between the two groups [RR 95% CrI: 0.73 (0.35-1.35)]. (**Supplement Figures 11-13**)

3.3.6. *Mortality before discharge*

Meta-analysis of observational studies showed that the risk of mortality before discharge was decreased in DRCPAP group when compared to oxygen supplementation group [RR 95% CI: 0.51 (0.42-0.62)]. (**Figure 2D**) Network estimates from RCTs did not reveal any statistically

significant difference between the two groups [RR 95% CrI: 0.98 (0.23-2.79)]. (**Supplement Figures 14-16**)

3.3.7. *IVH \geq Grade II*

Pooled estimates from two observational studies showed a trend towards decreased risk of IVH in DRCPAP group when compared to oxygen inhalation group [RR 95% CI: 0.86 (0.67-1.09)]. (**Supplement Figure 4D**) The network estimate did not show any statistically significant difference between any of the interventions. (**Supplement Figures 17-19**)

3.4. RoB and CoE

The RoB and CoE for given in **Supplement Figures 20-22 and Supplement Tables 3-4**, respectively.

4. DISCUSSION

Very low CoE from observational studies included in this review suggest that DRCPAP might be beneficial in decreasing the need of any invasive ventilation when compared to standard management including oxygen inhalation. Similar findings were reported by Zubizarreta et al. in their multi-centric study involving 25 South American NICUs and Afjeh et al in their single center study, both of which could not be synthesized in a meta-analysis in our review.^{29,39} The relative risk reduction for the outcome was much higher as evaluated by Zubizarreta et al. when compared to our meta-analysis. This could be attributed to the fact that Zubizarreta et al.'s study had matched the two groups utilizing a robust statistical tool compared to the other studies included in this meta-analysis. Also, while the former study adjudged the effect of prophylactic DRCPAP with relatively homogenous care practices which were implemented in their network NICUs, the studies included in our meta-analysis were from different countries with varying resources and DRCPAP protocols and had used DRCPAP both as a rescue and prophylactic strategy. Our results are also in agreement with Schmölzer et al.'s meta-analysis of DRCPAP use from HICs.⁴⁷

Moderate CoE from the network meta-analysis of RCTs and very low CoE from the synthesis of observational studies included in this systematic review showed that DRCPAP might be beneficial in decreasing the requirement of surfactant replacement therapy when compared to standard management. Similar results were also reported by Schmölzer et al.⁴⁷ These findings are of more relevance in the context of LMICs where surfactant use is limited by several factors.⁴⁸⁻⁴⁹ Analysis of clinical outcomes from the meta-analysis of observational studies in this systematic review revealed that DRCPAP might be effective in decreasing the risk of critical outcomes of BPD or mortality with a low CoE. Similar findings were also reported by Zubizarreta et al. in their multi-centric study and Schmölzer et al. in their meta-analysis.^{39,47} However, moderate CoE from RCTs indicate that neither DRCPAP or other interventions such as oxygen supplementation and surfactant use with DRCPAP showed any significant reduction of the combined outcome of mortality or BPD when compared to one another. The meta-analysis of DRCPAP studies from HICs had however shown a decreased risk of mortality or BPD.⁴⁷ It should be noted that whilst Schmölzer et al.'s review had included extremely low gestational age neonates; our analysis was based on studies that had predominantly included very preterm and VLBW neonates. Also, the comparator arm evaluated in Schmolzer et al.'s review was intubation followed by invasive ventilation.

Moderate CoE from our meta-analysis indicate that routine administration of DR surfactant along with DRCPAP might not decrease the risk of invasive ventilation or decrease the combined outcome of mortality or BPD when compared to DRCPAP alone. Isayama et al. in their meta-analysis had reported a trend towards early INSURE being beneficial when compared to CPAP alone in decreasing the risk of combined outcome of mortality or BPD at 36 weeks' gestational age.⁵⁰ While Isayama et al. had included studies that had enrolled neonates at different time periods from immediately after birth till 72 hours of postnatal age, we had looked at CPAP initiation or surfactant administration very early in the delivery room.⁵⁰

While evaluating the barriers to introducing DRCPAP, it was seen that despite best efforts towards policy change and dissemination of standard protocols, implementing DRCPAP is often faced with difficulties in LMICs. Trevisanuto et al. in their attitude survey of local health care providers from a WHO workshop had reported many important interventions that could aid in improving delivery room care in LMICs including education, doctor-nurse/patient ratio and equipment, many of which are of relevance for the implementation of DRCPAP as well.⁵¹ Similar constraints were also adjudged by Boo et al. in their survey where they had indicated that unavailability of compressed air and oxygen, absence of a standard policy and dearth of CPAP units were the most important reasons that precluded the utilization of DRCPAP.³⁷

Two studies that had evaluated ELBW neonates as a subgroup had reported a higher DRCPAP failure rate of 85-100% in the delivery room or NICU.^{31,33} CPAP failure rate as outlined by these studies is much higher than that reported by the large multi-centric RCTs from HICs which was about 65%.⁴⁷ The ELBW included in Kirsten et al.'s study from South Africa had a CPAP failure rate paralleling those from HICs.³⁴ Antenatal receipt of corticosteroids was higher in Kirsten et al.'s study and the RCTs from HICs when compared to those from LMICs. Also, much higher CPAP pressures (up to 8 cm H₂O) were used in some of the RCTs from HICs when compared to those from LMICs.⁴⁷ Whether the discrepancy in the DRCPAP failure rate is attributable only to differences in the antenatal steroid coverage or other practices related to optimal delivery of DRCPAP in LMICs were also contributory is a point to ponder.

Barring very few practices, most of the evidence-based practices related to neonatal care in LMICs are based on high quality research from HICs.^{52,53,54,55} It is to be emphasized that some of the practices proven to be effective in HICs might not be generalizable to LMIC settings. For example, use of therapeutic hypothermia which is a standard of care for neonates with moderate to severe hypoxic ischemic encephalopathy in HICs has been a subject of debate in LMICs.⁵⁶ Similarly, interventions such as DRCPAP need to be studied more rigorously in LMICs.

There were several limitations in this systematic review. There was wide heterogeneity in the sickness profile of the enrolled neonates. Limited number of included studies and their restricted reporting precluded multiple planned sensitivity analyses. Finally, though we aimed to look at the barriers of DRCPAP in LMICs, we did not find enough studies reporting it.

5. CONCLUSION

Very low CoE from limited number of observational trials indicate that DRCPAP might be beneficial in reducing the requirement of invasive ventilation when compared to oxygen supplementation. Also, moderate CoE from RCTs suggests that DRCPAP might decrease the requirement of surfactant therapy when compared to oxygen supplementation. Since future RCTs with oxygen supplementation as a comparator arm might not be appropriate, we suggest further multi-center observational studies from neonatal networks of LMICs with a before-after design and incorporating a robust methodology.

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FIGURE LEGENDS

Figure 1: Literature search flow

Figure 2: Forest plot depicting the estimates from meta-analysis of observation studies for the outcomes – 2A. Requirement of mechanical ventilation; 2B. Need for surfactant; 2C. Mortality or BPD at 36 weeks' PMA; 2D. Mortality before discharge

Figure 3: Network meta-analysis of RCTs for the primary outcome requirement of invasive mechanical ventilation - 3A. Network plot; 3B. SUCRA Plots, 3C. Forest plot with 'Oxygen inhalation' as common comparator

Figure 4: League plot depicting the effect estimates of different interventions for the primary outcome requirement of invasive mechanical ventilation

Figure 5: Pair-wise random effects meta-analysis of RCTs for the primary outcome requirement of invasive mechanical ventilation