OPEN ACCESS Freely available online

Pediatrics & Therapeutics

ISSN: 2161-0665

Research Article

Evaluate the Efficacy and Safety of Lucinactant in Preventing Bronchopulmonary Dysplasia (BPD) in Premature Infants

Alaa Abuzaid[1*], Shadi Noaman Garrada[2]

[1]Department of Pediatrics, King Hamad University Hospital, Muharraq,Bahrain; [2]Department of Neonatal, King Fahad Specialist Hospital, Dammam, Saudi Arabia

ABSTRACT

Aim: To evaluate the efficacy and safety of Lucinactant in preventing Bronchopulmonary Dysplasia (BPD) in premature infants.

Methods: The article included eight studies on the use of Lucinactant in preventing BPD in premature infants. Three of the four studies were published clinical trials and four were registered protocols without yet-published results. The article included 1281 participants from 8 clinical trials, of whom 137 received nCPAP only, 1016 received Lucinactant and 128 received other therapies.

Results: The article found that the evidence on the efficacy of Lucinactant in preventing BPD is mixed and vague . As Some studies have shown that Lucinactant is effective in reducing the incidence of BPD, while others have not. The article also found that Lucinactant may be associated with a lower mortality rate than other surfactant therapies. However, more researches are needed to confirm these finding.

Conclusion: The evidence of the systematic review on the use of Lucinactant in preventing Bronchopulmonary Dysplasia (BPD) in premature infants is not entirely conclusive, as some studies have found no significant differences in overall efficacy. Other one suggest that lucinactant may decrease the risk of BPD in Premature Infants.Further randomized prospective studies are necessary to evaluate this type of surfactant and to investigate its efficacy and both short- and long-term outcomes.

Keywords: Lucinactant; Surfactant Protein-B; Postmenstrual age

Abbreviations: RDS: Respiratory Distress Syndrome; BPD: Bronchopulmonary Dysplasia; MMPs: Matrix Metalloproteinases; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

INTRODUCTION

Preterm birth is worsened by RDS, a life-threatening illness in this population. Deficits in the lung surfactant pool are linked to reduced lung compliance and newborn RDS in preterm infants [1]. Furthermore, deficiencies in antioxidants and anti-inflammatory modulators have been linked to the progression of RDS and the development of chronic lung illness, most notably BPD [2-5].

RDS requires life-sustaining therapy, including supplementary oxygen and mechanical ventilation. These therapies have been demonstrated to harm the lungs and are linked to the aetiology of BPD [6]. Surfactant replacement therapy has become the gold standard in the prevention and treatment of RDS [7,8]. Surfactant replacement therapy, while beneficial in improving lung mechanics, oxygenation and mortality, has been associated to increased inflammatory responses and has had no meaningful impact on the incidence of BPD [9,10].

Lung inflammation is important to the pathophysiology of BPD in RDS and it is a complex process including the overexpression of pro-inflammatory cytokines such as IL-6 and IL-8, as well as the influx of inflammatory cells into the airways [11]. Deficits in antioxidants and anti-inflammatory modulators throughout infancy favor a pro-inflammatory process that promotes epithelial damage and lung remodeling *via* activated Matrix Modelling Proteins such as MMPs. MMPs generated by wounded cells increase microvascular permeability and release matrix components that act as pro-inflammatory mediators or growth factors, contributing to additional inflammation and remodeling [12]. MMP activity in the lung and airways has been linked to fibrotic lung disorders such as BPD [13,14].

Recently, surfactant-associated proteins perform critical functions in pulmonary homeostasis [15]. Surfactant-associated protein deficiency induces severe respiratory distress and, in the case of Surfactant Protein-B (SP-B), is fatal [16]. SP-B is a hydrophobic protein that reduces alveolar surface tension and may also have a role in host defense [17]. Lucinactant (Discovery Laboratories, Inc.,

Correspondence to: Alaa Abuzaid, Department of Pediatrics, King Hamad University Hospital, Muharraq,Bahrain, Tel: +9732256894; E-mail: alaaabouzeid2811@gmail.com

Received: 05-Nov-2024; Manuscript No. PTCR-24-34962; **Editor assigned:** 07-Nov-2024; PreQC No. PTCR-24-34962 (PQ); **Reviewed:** 21-Nov-2024; QC No. PTCR-24-34962; **Revised:** 28-Nov-2024; Manuscript No. PTCR-24-34962 (R); **Published:** 05-Dec-2024, DOI: 10.35248/2161-0665.24.14.590

Citation: Abuzaid A, Garrada NS (2024). Evaluate the Efficacy and Safety of Lucinactant in Preventing Bronchopulmonary Dysplasia (BPD) in Premature Infants. Pediatr Ther. 14:590.

Warrington, PA) is a synthetic surfactant formulation that contains Sinulpeptide (KL4) at a concentration comparable to that seen in human surfactant. KL4 is a 21 amino acid peptide consisting of one Lys and four Leu (KLLLLKLLLLKLLLLKLLLLK) that functionally replicates SP-B [18,19]. Lucinactant may provide anti-inflammatory protection over animal-derived surfactant formulations since surfactant proteins are present in relatively low concentrations. In our study, we aim to systemically review the role of Lucinactant in RDS.

MATERIALS AND METHODS

Study design and participants

This meta-analysis was designed and conducted in accordance with the PRISMA guidelines and the Cochrane Handbook of Systematic Reviews of Interventions [20].

Literature search

We conducted a comprehensive literature search of PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus and Web of Science for articles published between Jan 1, 1977 and Sep 1, 2023, without any other restrictions. We used the Medical Subject Headings (MeSH) database to develop our search strategy, which combined the following keywords and their related terms: Lucinactant, AeroSurf, Surfaxin®. The detailed search strategy is provided in Supplementary File.

Eligibility criteria and studies selection

The inclusion criteria included Randomized Controlled Trials (RCTs) evaluating the efficacy and safety of Lucinactant on neonates. No restrictions regarding the date of publication. Protocols published in clinicaltrials.gov were included if they contain results and sufficient information to assess their quality.

We removed papers that did not have enough data for extraction. Book reviews, book chapters, thesis editorials, letters, conference papers and non-English studies are all acceptable. Excluded studies included animal or *in vitro* research, cohort, case-control, non-clinical investigations, literature reviews and meta-analysis.

On an excel sheet, two separate writers reviewed the papers collected from the four electronic databases for eligibility using the title, abstract and full text. Any differences between the other two authors were settled by another independent author.

Quality assessment

The quality of the selected RCTs was assessed using the Cochrane risk-of-bias tool for randomized trials RoB [21]. The RoB 2 tool consists of domains including: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selection bias and other bias. The evaluators rated each domain as yes, probably yes, probably no, no, or no information. Any disagreements were discussed and resolved.

Data extraction and study outcomes

Two independent author's independently extracted data into a pre-defined excel spreadsheet. The spreadsheet items were categorized as a summary of the included trial's key features, characteristics of the participants and Lucinactant safety and efficacy outcomes. Any disagreements were resolved through discussion between the reviewers.

Outcome definition

Treatment efficacy was assessed by peri-dosing adverse events, BPD, mortality, complications of prematurity, air leak, worsening of respiratory status, oxygen saturation levels, FiO_2 and PCO_2.

Data collection and results

Our search retrieved 269 records from PubMed, Scopus, Web of Science, Cochrane Library, ClincalTrilas.gov and manual search. We removed 75 duplicates. After title and abstract screening, we eliminated 180 records. We then screened 14 studies for eligibility and excluded 6 studies. Four studies were protocols without results, two were without full texts available. Finally, we included eight records in our study: Four published clinical trials and four registered protocols from ClinicalTrials.gov (Figure 1).

The overall number of participants in this meta-analysis was 1281 (137 received nCPAP only, 1016 received Lucinactant and 128 received other therapies). A comprehensive summary of the listed research is provided in Table 1 depicts the characteristics of the subjects.

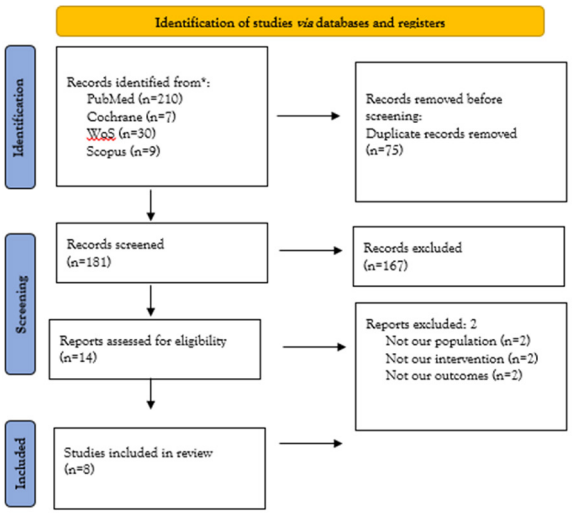

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Table 1: The characteristics of the subjects.

Study ID	Year	Country	Study design	Intervention	Comparator	Conclusion
Finer et al. [22]	2010	USA	RCT	Aerosurf® combined with nCPAP	nCPAP alone	The combination of Aerosurf® and nCPAP is safe and effective in preventing RDS in preterm neonates.
Laughon et al. [24]	2009	USA	RCT	Lucinactant	nCPAP, or mechanical ventilation	Lucinactant is safe and may be effective in preventing BPD in preterm infants who are already on mechanical ventilation. More research is needed to confirm these findings.
Moya et al. [25]	2007	USA and Europe	RCT	Lucinactant	Animal-derived surfactants, such as colfosceril palmitate (Exosurf®) and beractant (Survanta®)	Lucinactant is safe and effective in preventing RDS in very preterm infants and it is associated with better long-term outcomes than animal-derived surfactants.
Sinha et al. [23]	2005	USA, Canada and Europe	RCT	Lucinactant	Poractant alfa (Curosurf®), an animal-derived surfactant	Lucinactant is as effective as poractant alfa in preventing RDS in very premature infants at high risk for RDS. Lucinactant is also associated with a lower rate of BPD at 36 weeks' postmenstrual age.
NCT02528318		USA	RCT–open label	Lucinactant	nCPAP alone	Lucinactant is safe and effective in preventing RDS in preterm infants. The study found that the rate of RDS was lower in the lucinactant group (12.5%) than in the nCPAP group (37.5%). The difference was statistically significant.
NCT04264156		-	RCT	Lucinactant	nCPAP alone	Lucinactant is safe and effective in preventing RDS. However, the results of this trial is not reliable due to early termination of the study
NCT02074059		-	REC-open label	Lucinactant	nCPAP alone	-
NCT02636868		India	-	Lucinactant	nCPAP alone	-

RESULTS

Quality assessment results

Figures 2 and 3, shows a summary of the risk of bias. Concerning the randomization process bias, all of the studies were considered low risk in terms of the randomization process, with the exception of NCT03550378, which was deemed to have some concerns due to insufficient information about allocation concealment, randomization and baseline balance.

Regarding the random sequence generation (selection bias), most of included studies had low risk of bias except which designed as open label study and in which the randomization process was based on the birth weight of the infants [22,23]. In addition, both NCT02528318 and NCT02074059 was reported as high risk of bias due to their design as an open label trial.

Regarding the allocation concealment (selection bias), most of included studies had low risk of bias except for, NCT02528318 and NCT02074059 which designed as open label studies [22]. Furthermore, the treatment assignment was accomplished with sequentially numbered, opaque, sealed, drug identification envelopes and reported as low risk of bias [23].

Regarding blinding of participants and personnel (performance bias), most of included studies had low risk of bias except for, NCT02528318 and NCT02074059 which designed as open label studies [22]. Furthermore, to ensure masking, an independent dosing/drug preparation team not involved in the infant's medical treatment was designated at each site in the study done by Sinha et al., reported as low risk of bias [23].

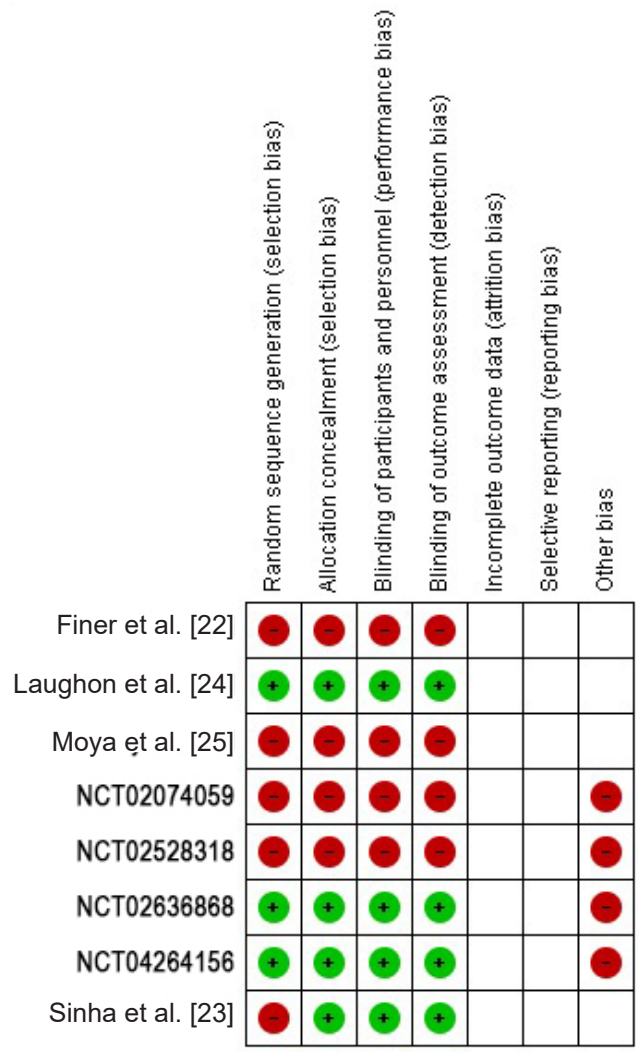

Figure 2: Risk of bais graph.

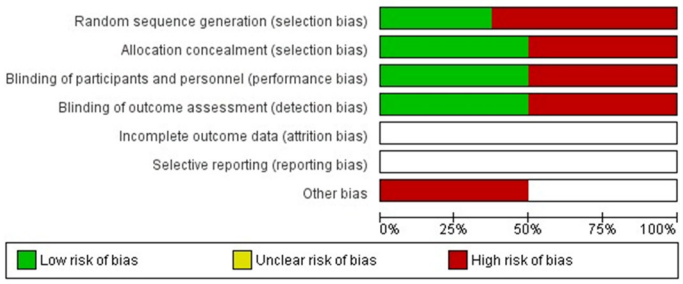

Figure 3: Risk of bais summary.

Regarding blinding of outcome assessment (detection bias), most of included studies had low risk of bias except which designed as open label study and in which the randomization process was based on the birth weight of the infants [22,23]. In addition, both NCT02528318 and NCT02074059 was reported as high risk of bias due to their design as an open label trial.

For the incomplete outcome data (attrition bias), all of included studies reported as some concerns. In addition, the risk of bias due to the selection of the reported results ranged from low to some concerns about the selection of the reported results bias. We rated all of the registered protocols as having some concerns because there is no available data to compare them to. The published trials posed little risk because all of the outcomes listed in the results were included in the procedures.

Efficacy endpoints

Bronchopulmonary Dysplasia (BPD): A study by Finer et al., reported that the BPD was detected in two (11.8%) newborns at 28 days [22]. In addition, a study by Laughon et al., found that Lucinactant was associated with a significant reduction in the incidence of death or BPD at 36 week's PMA [24]. The absolute risk reduction was 14% and the 90% CIs were 27.3% to 0.72%. Besides, a study by Moya et al., reported that Lucinactant and poractant alfa were administered at similar phospholipid doses (175 mg/kg) [25]. The primary outcome of being alive without BPD at 28 days was more frequent in the Lucinactant group (37.8%) than in the poractant alfa group (33.1%), but the difference was not statistically significant. While, the Sinha et al., study reported that the incidence of being alive without BPD at 28 days of age was higher in the Lucinactant group (37.8%, 95% CI: 29.1%-46.5%) than in the poractant alfa group (33.1%, 95% CI: 24.8%-41.3%) [23].

Furthermore, a higher rate incidence of live without BPD (87.5%-100%) was reported in NCT02528318 in compared to those who used nCPAP alone (75%). In contrast, the rate of incidence was almost similar to those in the NCT02636868 (88.6%) *vs.* (83.1%) in nCPAP alone group. Furthermore, no difference was found between the both groups in NCT04264156 and no reported data was found in the NCT02074059.

Mortality: A study by Laughon et al., reported that the mortality or BPD rate was 66% in the placebo group, 79% in the 90 mg/kg group and 58% in the 175 mg/kg group with no statistically difference between the different sites of the study [24]. Combined data from two trials of a study by Moya et al., showed a lower mortality rate in infants who received Lucinactant than in those who received animal-derived surfactants (20.1% *vs.* 24.7%; p=0.045; OR=0.70; 95% CI: 0.50-0.99) [25]. Besides, a Sinha et al., study reported that Lucinactant was associated with a lower mortality rate than poractant alfa at 28 days (11.8% *vs.* 16.1%) and 36 week's postmenstrual age (16% *vs.* 18.5%), [23].

Furthermore, a higher rate incidence of mortality (12.5%) was reported in NCT02528318 in compared to those who used nCPAP alone (0%). In contrast, the rate of incidence was (12.5%) in nCPAP alone group NCT02074059 than Lucinactant group. No reported data was found regrading both NCT02636868 and NCT04264156.

DISCUSSION

This systematic review identified eight studies on the use of Lucinactant in preventing BPD in premature infants. Three of four studies were published clinical trials and four were registered protocols without yet-published results. Our study included 1281 participants from 8 clinical trials, of whom 137 received nCPAP only, 1016 received Lucinactant and 128 received other therapies.

Several studies have investigated the efficacy of Lucinactant in preventing BPD in premature infants. A study by Finer et al., found that the incidence of BPD at 28 days was 11.8% in infants who received Lucinactant [22]. A study by Laughon et al., found that Lucinactant was associated with a significant reduction in the incidence of death or BPD at 36 weeks' Postmenstrual Age (PMA),

with an absolute risk reduction of 14% [24]. A study by Moya et al., found that Lucinactant and poractant alfa were administered at similar phospholipid doses, but the primary outcome of being alive without BPD at 28 days was more frequent in the Lucinactant group (37.8%) than in the poractant alfa group (33.1%), but the difference was not statistically significant [25]. A study by Sinha et al., found that the incidence of being alive without BPD at 8 days of age was higher in the Lucinactant group (37.8%) than in the poractant alfa group (33.1%) [23].

More recent studies have also shown promising results. A registered clinical trial (NCT02528318) reported a higher rate of incidence of live without BPD (87.5%-100%) in infants who received Lucinactant compared to those who received nCPAP alone (75%). However, another registered clinical trial (NCT02636868) found that the rate of incidence was almost similar between the Lucinactant group (88.6%) and the nCPAP alone group (83.1%). No difference was found between the two groups in NCT04264156 and no data was reported in NCT02074059.

A published randomized controlled trial by Morley et al., evaluated the early use of nCPAP in preventing BPD in premature infants with a gestational age of 27-28 weeks [26]. The study found that the survival rate without BPD was 48.6% in the nCPAP alone group and the incidence of pneumothorax was 9.1%. In addition, the study found that the survival rate without BPD was 83.3% in the AeroSurf group and there was no incidence of pneumothorax.

Discussion several studies have investigated the effect of Lucinactant on mortality in premature infants. A study by Laughon et al., found that the mortality or BPD rate was 66% in the placebo group, 79% in the 90 mg/kg group and 58% in the 175 mg/kg group, with no statistically significant difference between the different sites of the study [24]. A study by Moya et al., combined data from two trials and found a lower mortality rate in infants who received Lucinactant than in those who received animal-derived surfactants (20.1% *vs.* 24.7%; p=0.045; OR=0.70; 95% CI: 0.50-0.99) [25].

A study by Sinha et al., also found that Lucinactant was associated with a lower mortality rate than poractant alfa at 28 days (11.8% *vs.* 16.1%) and 36 weeks' postmenstrual age (16% *vs.* 18.5%) [23]. More recent studies have also shown promising results. A registered clinical trial (NCT02528318) reported a higher rate of incidence of mortality (12.5%) in infants who received nCPAP alone compared to those who received Lucinactant (0%).

However, another registered clinical trial (NCT02074059) found that the rate of incidence of mortality was higher in the nCPAP alone group (12.5%) than in the Lucinactant group (0%). No data was reported regarding mortality in the NCT02636868 and NCT04264156 trials.

Overall, future studies on the use of Lucinactant to prevent BPD and mortality in premature infants should be prospective and randomized. This would allow for the establishment of causality and would help to rule out the potential confounding effects of other factors.

CONCLUSION

The conclusion of the systematic review on the use of Lucinactant in preventing Bronchopulmonary Dysplasia (BPD) in premature infants is that the evidence is mixed. Some studies have shown that Lucinactant is effective in reducing the incidence of BPD, while others have not. More research is needed to confirm the efficacy of Lucinactant in preventing BPD in premature infants.

COMPETING INTERESTS

The authors declare that they have no competing interests.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest related to this study.

REFERENCES

1. Jobe AH, Ikegami M, Jacobs HC, Jones SJ. Surfactant pool sizes and severity of respiratory distress syndrome in prematurely delivered lambs. Am Rev Respir Dis. 1983;127(6):751-755.
2. Falciglia HS, Johnson JR, Sullivan JA, Hall CF, Miller JD, Riechmann GC, et al. Role of antioxidant nutrients and lipid peroxidation in premature infants with respiratory distress syndrome and bronchopulmonary dysplasia. Am J Perinatol. 2003;20(02):97-108.
3. Mentro A. Vitamin A and bronchopulmonary dysplasia: Research, issues and clinical practice. Neonatal Netw. 2004;23(4):19-23.
4. Splawski JB, Yamamoto K, Lipsky PE. Deficient interleukin-10 production by neonatal T cells does not explain their ineffectiveness at promoting neonatal B cell differentiation. Eur J Immunol. 1998;28(12):4248-4256.
5. Loughran-Fowlds A, Oei J, Wang H, Xu H, Wimalasundera N, Egan C, et al. The influence of gestation and mechanical ventilation on serum clara cell secretory protein (CC10) concentrations in ventilated and nonventilated newborn infants. Pediatr Res. 2006;60(1):103-108.
6. Chess PR, D'Angio CT, Pryhuber GS, Maniscalco WM. Pathogenesis of bronchopulmonary dysplasia2006: Elsevier. Semin Perinotol. 2006;30(4):171-178.
7. Clement A. Bronchopulmonary dysplasia. Rev Mal Respir. 1996;13(3):243-249.
8. Bhandari A, Bhandari V. Pathogenesis, pathology and pathophysiology of pulmonary sequelae of bronchopulmonary dysplasia in premature infants. Front Biosci. 2003;8(5):370-380.
9. Hilgendorff A, Rawer D, Doerner M, Tutdibi E, Ebsen M, Schmidt R, et al. Synthetic and natural surfactant differentially modulate inflammation after meconium aspiration. Intensive Care Med. 2003;29:2247-2254.
10. Meyer KC, Zimmerman JJ. Inflammation and surfactant. Paediatr Respir Rev. 2002;3(4):308-314.
11. de Dooy JJ, Mahieu LM, van Bever HP. The role of inflammation in the development of chronic lung disease in neonates. Eur J Pediatr. 2001;160:457-463.
12. Bakowska J, Adamson IYR. Collagenase and gelatinase activities in bronchoalveolar lavage fluids during bleomycin-induced lung injury. J Pathol. 1998;185(3):319-323.
13. Danan C, Jarreau P-H, Franco M-L, Dassieu G, Grillon C, Alsamad IA, et al. Gelatinase activities in the airways of premature infants and development of bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol. 2002;283(5):L1086-L1093.
14. Corbel M, Belleguic C, Boichot E, Lagente V. Involvement of gelatinases (MMP-2 and MMP-9) in the development of airway inflammation and pulmonary fibrosis. Cell Biol Toxicol. 2002;18:51-61.
15. Whitsett JA. The intersection of surfactant homeostasis and innate host defense of the lung: Lessons from newborn infants. Innate Immun. 2010;16(3):138-142.
16. Nogee LM, Wert SE, Proffit SA, Hull WM, Whitsett JA. Allelic heterogeneity in hereditary surfactant protein B (SP-B) deficiency. Am J Respir Crit Care Med. 2000;161(3):973-981.
17. Frerking I, Günther A, Seeger W, Pison U. Pulmonary surfactant: Functions, abnormalities and therapeutic options. Intensive Care Med. 2001;27:1699-1717.

18. Revak SD, Merritt TA, Cochrane CG, Heldt GP, Alberts MS, Anderson DW, et al. Efficacy of synthetic peptide-containing surfactant in the treatment of respiratory distress syndrome in preterm infant rhesus monkeys. Pediatr Res. 1996;39(4):715-724.

19. Wiswell TE, Smith RM, Katz LB, Mastroianni L, Wong DY, Willms D, et al. Bronchopulmonary segmental lavage with surfaxin (KL4-surfactant) for acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160(4):1188-1195.

20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Intern J Surgery. 2021;88:105906.

21. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions. 2019:205-228.

22. Finer NN, Merritt TA, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf® combined with nCPAP to prevent RDS in preterm neonates. J Aerosol Med Pulm Drug Deliv. 2010;23(5):303-309.

23. Sinha SK, Lacaze-Masmonteil T, Valls i Soler A, Wiswell TE, Gadzinowski J, Hajdu J, et al. A multicenter, randomized, controlled trial of lucinactant *versus* poractant alfa among very premature infants at high risk for respiratory distress syndrome. Pediatrics. 2005;115(4):1030-1038.

24. Laughon M, Bose C, Moya F, Aschner J, Donn SM, Morabito C, et al. A pilot randomized, controlled trial of later treatment with a peptide-containing, synthetic surfactant for the prevention of bronchopulmonary dysplasia. Pediatrics. 2009;123(1):89-96.

25. Moya F, Sinha S, Gadzinowski J, D'Agostino R, Segal R, Guardia C, et al. One-year follow-up of very preterm infants who received Lucinactant for prevention of respiratory distress syndrome: Results from 2 multicenter randomized, controlled trials. Pediatrics. 2007;119(6):e1361-e1370.

26. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet J-M, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358(7):700-708.