Comparison of Porcine Versus Bovine Surfactant in preterm respiratory distress syndrome: Evidence from real world data. A multicenter collaboration from Karnataka

Abhishek Aradhya [1], Sharath Ghalige S[1], Babu Madarkar[2], Pruthvishree HV[3], Praveen Venkatagiri[4], Prashant Urs[5], Daizy Ngangom[2], Sandeep Rangaiah[1], Vimal Kumar[3], Chinnaraja Harini[4], Arpna Bansal[5], and Maneesha Halkar P[1]

[1]Ovum Hospitals
[2]Rainbow Children's Hospital and BirthRight by Rainbow Marathahalli
[3]Ovum Woman & Child Speciality Hospital Banaswadi
[4]Chinmaya Mission Hospital
[5]Apollo Hospitals Bannerghatta

June 12, 2023

Abstract

BACKGROUND & OBJECTIVES: Porcine surfactant (200 mg/kg initial dose) seems to be superior over bovine surfactants (100 mg/kg) in respiratory distress syndrome (RDS). There is limited data on choice of surfactant from the developing world. Logically using higher doses of porcine surfactant comes with additional burden of cost. We decided to evaluate the clinical effect of different types of surfactants. **METHODS:** A retrospective analysis was conducted from August 2019 to December 2022 in 6 tertiary centres. Neonates 24-34 weeks of gestation with RDS requiring either porcine (200 mg/kg) or bovine surfactant (100 mg/kg) were enrolled. The proportion of combined outcomes of death and or CLD, redosing and other morbidities in either group were analysed. The subgroup of preterm >28 weeks and outcomes between different surfactants were analysed. **RESULTS:** Out of 1149 eligible babies, 302 (26%) received surfactant after stabilisation with CPAP. 158 received porcine and 144 received bovine surfactant via INSURE technique. There was a higher combined outcome of death or CLD in porcine compared to the bovine group [48 (30%) vs 20 (13%), OR:2.7; 95% CI:1.5-4.8; p=0.001] and similar combined outcomes in >28 weeks sub-group. Redosing [27 (17%) Vs 18 (12%), OR:1.4; 95% CI:0.7-2.7; p=0.2] was similar. Other morbidities like air leak, invasive ventilation, CPAP duration were similar between both the groups and different types of surfactants. **CONCLUSION:** Porcine surfactant at 200mg/kg had similar combined outcomes of death/ CLD and redosing compared to bovine surfactant in preterm >28 weeks. Considering the cost burden in the developing world, the efficacy needs evaluation in randomised clinical trials.

Title: Comparison of Porcine Versus Bovine Surfactant in preterm respiratory distress syndrome: Evidence from real world data. A multicenter collaboration from Karnataka

Authors: Sharath S Ghalige[1], Abhishek S Aradhya[2], Babu Madarkar[3], Pruthvishree HV[4], Praveen Venkatagiri[5], Prashant Urs[6], Daizy Ngangom[3], Sandeep Rangaiah[2], Vimal Kumar[4], Chinnaraja Harini[5], Arpna Bansal[6], Maneesha P Halkar[1]

Affiliations: 1- Department of Pediatrics, Ovum Woman & Child Specialty Hospital, Banashankari; 2- Department of Pediatrics, Ovum Woman & Child Specialty Hospital, Hoskote, Bangalore rural; 3- Department of Pediatrics, Rainbow Children's Hospital, Bangalore; 4- Department of Pediatrics, Ovum Woman & Child

Specialty Hospital, HRBR layout; 5-Department of Pediatrics, Chinmaya Mission Hospital, Bangalore; 6-Department of Pediatrics, Apollo hospital, Bannerghatta Road, Bangalore.

Corresponding Author:

Dr Abhishek S Aradhya

Consultant Neonatologist and Pediatrician

Ovum Woman and Child Specialty Hospital,

Hoskote, Bangalore-562114

Email: abhishekaradhyas@gmail.com

ORCID ID: 0000-0003-3524-0939

Abbreviations: RDS-Respiratory distress syndrome, CPAP- Continuous positive airway pressure, INSURE- Intubate Surfactant Extubate, OR- Odds ratio, SD- standard deviation, CLD- Chronic lung disease.

Keywords: Surfactant types, preterm, RDS, Chronic lung disease

Funding: None

Ethical clearance: Ethical clearance obtained. (IRB no.RCHEC-01-2023)

Disclosure of Conflicts of Interest: None

Patient consent for publication: Not required

Word Count: Main text: 2842 words Abstract: 255 words

Acknowledgement:

Data entry: Dr. Rosamma, Medical Officer, Chinmaya Mission Hospital, Bangalore

Contributors statement:

Sharath Ghalige: Designed data collection tool, data collection, assisted in data analysis,

drafted the initial manuscript and approved the final manuscript.

Abhishek S Aradhya: Conceptualized the study, supervised data collection, data analysis, assisted in drafting initial manuscript and approved final manuscript

Babu Madarkar: supervised data collection, assisted in data analysis and approved the final manuscript.

Pruthvishree HV: Designed data collection tool, data collection and approved final manuscript

Dr Praveen Venkatagiri, Prashant Urs: Supervised data collection, critical inputs to the manuscript and approved final manuscript.

Daizy Ngangom, Sandeep, Vimal Kumar, Chinnaraja Harini, Arpna Bansal, Maneesha PH: Data collection, critical inputs to the manuscript, approved final manuscript

Abstract

BACKGROUND & OBJECTIVES: Porcine surfactant (200 mg/kg initial dose) seems to be superior over bovine surfactants (100 mg/kg) in respiratory distress syndrome (RDS). There is limited data on choice of surfactant from the developing world. Logically using higher doses of porcine surfactant comes with additional burden of cost. We decided to evaluate the clinical effect of different types of surfactants.

METHODS: A retrospective analysis was conducted from August 2019 to December 2022 in 6 tertiary centres. Neonates 24-34 weeks of gestation with RDS requiring either porcine (200 mg/kg) or bovine surfactant (100 mg/kg) were enrolled. The proportion of combined outcomes of death and or CLD, redosing and other morbidities in either group were analysed. The subgroup of preterm >28 weeks and outcomes between different surfactants were analysed.

RESULTS: Out of 1149 eligible babies, 302 (26%) received surfactant after stabilisation with CPAP. 158 received porcine and 144 received bovine surfactant via INSURE technique. There was a higher combined outcome of death or CLD in porcine compared to the bovine group [48 (30%) vs 20 (13%), OR:2.7; 95% CI:1.5-4.8; p=0.001] and similar combined outcomes in >28 weeks sub-group. Redosing [27 (17%) Vs 18 (12%), OR:1.4; 95% CI:0.7-2.7; p=0.2] was similar. Other morbidities like air leak, invasive ventilation, CPAP duration were similar between both the groups and different types of surfactants.

CONCLUSION: Porcine surfactant at 200mg/kg had similar combined outcomes of death/ CLD and redosing compared to bovine surfactant in preterm >28 weeks. Considering the cost burden in the developing world, the efficacy needs evaluation in randomised clinical trials.

Study background and rationale

Respiratory Distress Syndrome (RDS) is a common cause of morbidity and mortality in preterm neonates, especially those <34 weeks of gestation. Though the cases of classical severe Hyaline Membrane Disease (HMD) are seen very less recently with the increasing usage of Antenatal Corticosteroid, a sizable number of preterm neonates do require Surfactant Replacement Therapy despite receiving best of the Delivery room practices including Continuous Positive Airway Pressure (CPAP).

Animal-derived Natural Surfactant preparations are the ones now recommended as standard of care practice for Surfactant replacement therapy in RDS[1]. Among these, bovine origin surfactant or Beractant (Survanta), Bovine Lung Extract Surfactant – BLES (Neosurf) and Porcine origin surfactant – Poractant α (Curosurf) are available for commercial use in India. There have been a few comparative studies evaluating natural surfactants. Results differ based on comprehensive newborn unit policies used for overall management of RDS. An important study among these, Ramanathan et al. compared the efficacy and safety of poractant alfa and beractant in preterm infants with RDS (3 groups: 100 mg/kg of poractant alfa, 200 mg/kg of poractant alfa, and 100 mg/kg of beractant). Mortality, redosing of surfactant, and oxygen supplements were significantly reduced in the 200 mg/kg of poractant alfa group than in the 100 mg/kg of poractant alfa or beractant groups[2]. However, it has also been reported that the timing of administration of the surfactant, such as prophylactic versus rescue and early (within 2 hours after birth) versus delayed (later than 2 hours after birth) treatment, is more important than the composition of the surfactant[3]. A recent meta-analysis in 2019, showed that poractant-α (at 200 mg/kg dose) is associated with better short term respiratory outcomes including lesser combined outcome of BPD/mortality when compared to bovine surfactants at their licensed dose (100 mg/kg) in preterm neonates with RDS[4]. The pooled analysis also showed an unusually high rate of redosing with bovine surfactant (45% vs 21%) compared to porcine, which is hardly seen in clinical practice. Most of these studies are a decade older, where the practice of antenatal steroids, delivery room CPAP, timing of surfactant, surfactant need (rescue/prophylactic) etc. were still evolving. Higher doses of Poractant- α will also incur higher cost. In contrast to meta-analysis, systematic review of studies of real-world evidence shows similar outcomes in both types of animal derived surfactant.[5] Also, there is limited evidence from the Indian subcontinent comparing the animal-derived natural surfactants in their standard prescribed doses in real world scenarios. Hence, the current study was planned to evaluate the effect of surfactant preparations in preterm RDS on various morbidities.

Material and methods

This retrospective study was conducted involving 6 tertiary care NICU of South India over a period from August 2019 to December 2022. Both inborn and outborn preterm neonates born between 24- 34 weeks of gestation having RDS and requiring rescue surfactant were enrolled. Exclusion criteria included babies with antenatally or postnatally suspected or diagnosed structural lung disease, major congenital malformations

and where death or discharge (against medical advice) or referred to other NICU occurred within 24 hours of life. The Institutional ethics committee approved the study at all centres.

Of the 6 tertiary centres that participated, one was a trust hospital, while the other 5 were private sector hospitals. All the centres catered to both inborn and outborn neonates. All the centres started delivery room CPAP with settings of 5 PEEP and 30% FiO2 using a T piece resuscitator in spontaneously breathing infants. Surfactant was administered predominantly using INSURE technique when the baby continued to have respiratory distress on settings of [?] 6 cm PEEP and FiO2 >30%.[1] All units either used porcine surfactant (Curosurf, Chiesi, USA Inc) at 200 mg/kg or bovine (Neosurf, Cipla/Survanta, Abbott) at 100 mg/kg. The choice of surfactant was individual clinician based, however there was inclination towards usage of porcine for extreme preterm owing to smaller volume of the dose. Redosing was considered when the baby continued to have respiratory distress needing [?] 6 cm PEEP and FiO2 >30%, after 12 hours of first dose. Nasal mask was used as a nasal interface in 5 centres and Ram's cannula was used in one centre. All centres had nurse:patient ratio of 1:2. Overall the protocols of managing RDS were similar across centres.

The data were identified from the unit specific registers/database. Case records of NICU admissions across the hospitals in the collaboration were retrieved. Data retrieved included demographic, antenatal, perinatal parameters related to RDS and neonatal morbidities and mortality. A standardised data collection proforma was used across all units. Data was entered into a common database with coding of the centres. Chronic lung disease (CLD) was defined as need for supplemental oxygen at 36 weeks i.e., moderate to severe CLD as per the NICHD criteria[6].

The primary outcome measure studied was combined outcome of Mortality or Chronic Lung Disease (CLD). The secondary outcome measures which were studied are proportion of babies requiring redosing of surfactant, Air leaks, invasive ventilation, ROP requiring LASER, PDA requiring treatment, Intraventricular hemorrhage (IVH) (>Grade 3 or 4), Necrotizing enterocolitis (NEC) (>Stage 2B) and duration of hospital stay.

Statistical analysis

The collected data was coded and entered to the Statistical Package for Social Science (IBM- SPSS v.25, SPSS Inc) for analysis. The variables listed were analysed and compared between the groups. The quantitative data were presented as mean and standard deviation when their distribution is parametric and as median and range when their distribution is nonparametric. Qualitative variables were presented as number, percentages, or proportions. The confidence interval was set to 95% and the margin of error accepted was set to 5%. P-value was considered significant if P [?] 0.05. Appropriate statistical tests were used to compare the variables. The confidence interval was set to 95% and P-value considered significant if P [?] 0.05. Subgroup analysis was done for gestation >28 weeks and between surfactant types (Curosurf, Survanta, Neosurf)

Results

Out of 1149 infants, between 24-34 weeks of gestation, 302 (26%) babies received surfactant after stabilisation with CPAP (rescue surfactant). 158 babies received porcine and 144 received bovine surfactant via INSURE technique. The mean gestation (standard deviation) of the enrolled babies were 29 (2) weeks. The mean birth weight (standard deviation) of the babies was 1270 grams (437). The demographic characteristics are summarised in table 1. At baseline, the porcine group had babies with lower gestation and birth weight and higher proportion of babies with completion of antenatal steroid course, lower APGARs, CLD, screen positive early onset sepsis, PDA requiring treatment; and longer length of stay compared to babies receiving any bovine surfactant. The combined outcome of death or CLD was statistically significant in porcine compared to the bovine group [48 (30%) vs 20 (13%), OR:2.7; 95% CI:1.5-4.8; p=0.001]. Redosing [27 (17%) Vs 18 (12%), OR:1.4; 95% CI:0.7-2.7; p=0.2] was similar in both the groups. Other important morbidities like duration of CPAP, invasive ventilation, air leak, severe IVH, ROP requiring LASER, NEC were similar.

Subgroup analysis of babies >28 weeks showed a similar rate of combined outcome of CLD/death [16 (14%) Vs 14 (10%), OR1.4; 95% CI:0.6-3; p=0.4. There was a higher proportion of screen positive early onset

sepsis and longer length of stay. Other morbidities like redosing, air leak, need for invasive ventilation and CPAP duration were similar between both the groups. The subgroup analysis is summarised in table 2.

On comparison of three different surfactant preparations, the CLD or combined outcome with CLD and mortality was higher in the porcine group compared to the other two bovine preparations. However, the porcine group had lower gestational age and weight. Other morbidities like redosing, air leak, need for invasive ventilation and CPAP duration was similar. The comparison is summarised in table 3.

Discussion

In our study there was a higher combined outcome of death or CLD in porcine compared to bovine groups [48 (30%) vs 20 (13%), OR:2.7; 95% CI:1.5-4.8; p=0.001]. This finding is unlike Cochrane review which found lesser mortality (in-hospital) in porcine group. Cochrane Meta-analysis done by Singh et.al. demonstrated a significant increase in death or oxygen requirement at 36 weeks' postmenstrual age (typical RR 1.30, 95% CI 1.04 to 1.64; typical RD 0.11, 95% CI 0.02 to 0.20; NNTH 9, 95% CI 5 to 50; 3 studies and 448 infants; moderate quality evidence) in bovine group compared to porcine group.[7]Systematic review by Tridente et.al. shows a trend favouring porcine groups as well[4]. In this review, 12 trials reported data on the composite BPD/mortality outcome, analysing poractant-α given at a dose of 200 mg/kg and another study evaluating poractant-α at a dose of 100mg/kg which showed significantly. The concept CLD has evolved over a period of time with changing definitions based on the pathophysiological understanding of the condition. Even after the widely used NICHD workshop definition which is used in our study, modifications are ongoing. [6,18-25] This finding is unlike Cochrane review which found lesser mortality (in-hospital) in porcine groups. Cochrane Meta-analysis done by Singh et.al. demonstrated a significant increase in death or oxygen requirement at 36 weeks' postmenstrual age (typical RR 1.30, 95% CI 1.04 to 1.64; typical RD 0.11, 95% CI 0.02 to 0.20; NNTH 9, 95% CI 5 to 50; 3 studies and 448 infants; moderate quality evidence) in bovine group compared to porcine group.[6] Systematic review by Tridente et.al. shows a trend favouring porcine groups as well[4]. In this review, 12 trials reported data on the composite BPD/mortality outcome, analysing poractant-α given at a dose of 200 mg/kg and another study evaluating poractant-α at a dose of 100mg/kg which showed significantly lower incidence in neonates treated with 200 mg/kg poractant-α ($p < 0.001$), and pooling together neonates treated with both doses ($p < 0.001$) compared to bovine surfactant.[4] The review by Luna et.al. which compares RWE and RCTs showed that the composite endpoint of BPD or death occurred with similar incidence in the beractant and poractant alfa groups in the two studies with RWE that reported this outcome.[5,9-12]

Moderate-Severe BPD, were more common among babies which received Porcine surfactant. This was unlike Cochrane review where no difference was found and in contrast to Tridente et.al. meta-analyses.[6,4] This could be due to the babies which received Porcine surfactant being smaller babies with average GA of 28 weeks compared with those who received bovine surfactant with average GA of 30 weeks ($p<0.001$), which inherently increases the chances of having BPD of any severity. This observation can also be seen to be coherent with the subgroup analysis of infants>28 weeks, which does not show a statistically significant difference in case of Moderate-Severe BPD. A real-world study by Paul S et.al. that compared the incidence of BPD with beractant and poractant alfa found no significant difference between treatments.[11]

In our study, the need for redosing of surfactant in RDS was not different between porcine and bovine surfactant in their standard initial dose (p=0.2). Subgroup analysis of infants of >28 weeks as well as individual surfactants did not show any difference(p=0.1). This is in contradiction with the meta-analyses by Tridente et.al.[4] where redosing was needed more often in the bovine group than in the porcine group with a statistically highly significant difference (p=0.001). The said study also concludes that the effect on the need for redosing is greater at higher gestational ages unlike what we found in our study. This could be likely attributed to the usage of studies well from 3 decades back when the supportive care for preterm babies who might have RDS was not standardised compared to the present day. Lanciotti L et.al. noted that if poractant alfa is used, need for re-dosing can be minimised by using a larger initial dose of 200 mg/ kg. For other surfactants, such data are not available.[8] As per The Cochrane review by Singh et.al. , significant increase in the incidence of 'receiving > 1 dose of surfactant' was noted in infants treated with modified bovine minced lung surfactant extract compared with porcine minced lung surfactant extract. Clinical equivalence

was noted with no significant differences in comparative trials between bovine lung lavage surfactant and modified bovine minced lung surfactants.[7]

In our study there was no difference in the duration of CPAP needed as well as Invasive ventilation needed (p=0.06 and p=0.6 respectively). Length of hospital stay was more in babies which received porcine surfactant (p<0.001). This may be due to the fact that porcine group babies compared to bovine groups were of a lower gestational age (28 weeks vs 30 weeks) and lower birth weight (1113 grams vs 1443 grams).

In our study we did not find any statistically significant difference for any pulmonary air leaks like Pneumothorax(p=1). This is in line with Cochrane review[7] but contrasts Tridente et.al. study[4] which concludes less chances of Air leak among porcine surfactant use. This could be due to understanding that the occurrence of air leaks may be more attributable to the lung tissue, sepsis, ventilatory strategies than the surfactant.

The occurrence ROP requiring LASER was similar in both bovine and porcine groups in our study(p=0.6). As per Cochrane review as well, no significant difference was found between surfactant preparations and occurrence of ROP needing LASER.[7]

PDA requiring treatment was noted to be more in porcine group (24%) compared to bovine group (12%) which was statistically significant (p=0.006). However, Cochrane reported no effect of surfactant preparation on risk of PDA requiring treatment with cyclooxygenase inhibitor or surgery.[7] In a study by Mussavi et.al. it was noted that in neonates over 32 weeks there was a significant difference between groups for the incidence rate of PDA (P = 0.011) but not below 32 weeks.[15] The smaller the gestation, the more chances of having a PDA needing treatment due to inherent prematurity related factors probably explains the occurrence in our study.

The study did not find a statistically significant difference between bovine and porcine groups with respect to IVH (of any grade) and more importantly IVH of Grade 3 or more. The Cochrane review also did not show demonstrable significant difference among the surfactant preparations on the risk of IVH (of any grades) as well as severe IVH of Grade 3 or more.[7]

The incidence of NEC in our study was no different than among bovine and porcine groups (p=0.6). Even the Cochrane review does not show any difference between the surfactant preparations with respect to occurrence of NEC of any stage.[7] In a study by Najafian et.al. they found that intraventricular haemorrhage (IVH) and necrotizing enterocolitis (NEC) are more frequent in the Curosurf group in comparison with Survanta in 29-32 weeks neonates. It was also realised that lower birth weight and lower gestation were associated with more complication in both groups.[16]

We chose retrospective data from December 2022 backwards to August 2019 as it was after an Update by European Consensus Guidelines on management of RDS[1] had been published and widely being discussed and adopted in our Neonatal units. A sub-group analysis of neonates > 28 weeks was chosen because these were babies who were candidates for less RDS, less CLD (or BPD) and other morbidities compared to those [?] 28 weeks. Also, there was an inclination towards porcine surfactant by some clinicians in [?] 28 weeks based on European consensus guidelines. Alongside subgroup analysis was done with all the 3 commercially available surfactants in India.

Limitations

As far as limitations of our study, apart from being a retrospective study from across 6 centres, an important limitation of our study is that we have not collected the data on pulmonary haemorrhage and its association with the type of surfactant used. Study by Tridente et.al. favours use of porcine surfactant which had noted lesser lung haemorrhage whereas the cochrane review showed no difference.[4,7] We felt lung haemorrhage having multiple etiologies in very small newborns including hemodynamically significant PDA, sepsis, DIC has more confounding factors and attributing it to type of surfactant type may not be easy in a retrospective design. Possibility of approximation of dose of surfactant due to more common whole-vial based dosing in place of exact weight-based dosing remains inherent limitation of retrospective study.[13]

Cost benefit analysis comparing the surfactant preparations has not been attempted owing to the varied hospital policies of billing. This precludes our assumption that bovine surfactant use may reduce the cost compared to porcine surfactants. Magni et.al. have noted that here were no significant differences in neonatal intensive care unit (NICU) length of stay or NICU total costs between infants treated with beractant (Survanta®), calfactant (Infasurf®) or poractant alfa (Curosurf®) in a study data from developed countries and funded by Chiesi Farmaceutici S.p.A.[14]

More data from a larger sample size, randomised controlled studies, from India may be needed to address the issues of type of surfactant usage in RDS with different morbidities and mortality.

Conclusion

Porcine surfactant at 200mg/kg had similar combined outcomes of death/ CLD and redosing compared to bovine surfactant in preterm >28 weeks. Considering the cost burden in the developing world, with no added advantage of using higher doses of porcine surfactant over bovine surfactant, there is an urgent need to evaluate the efficacy in randomised clinical trials.

References

1. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update. Neonatology. 2019;115(4):432-450.
2. Ramanathan R, Rasmussen MR, Gerstmann DR, Finer N, Sekar K; North American Study Group. A randomized multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. Am J Perinatol 2004;21:109-19
3. Lopez E, Gascoin G, Flamant C, Merhi M, Tourneux P, Baud O, et al. Exogenous surfactant therapy in 2013: what is next? Who, when and how should we treat newborn infants in the future? BMC Pediatr 2013;13:165
4. Tridente A, De Martino L, De Luca D. Porcine vs bovine surfactant therapy for preterm neonates with RDS: systematic review with biological plausibility and pragmatic meta-analysis of respiratory outcomes. Respir Res 2019;20:28
5. Sánchez Luna M, Bacher P, Unnebrink K, Martinez-Tristani M, Ramos Navarro C. Beractant and poractant alfa in premature neonates with respiratory distress syndrome: a systematic review of real-world evidence studies and randomized controlled trials. J Perinatol. 2020 Aug;40(8):1121-1134.
6. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am. J. Respir. Crit. Care Med. 2001; 163, 1723–1729
7. Singh N, Halliday HL, Stevens TP, Suresh G, Soll R, Rojas-Reyes MX. Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev. 2015;12: CD010249
8. Lanciotti L, Correani A, Pasqualini M, Antognoli L, Dell'Orto VG, Giorgetti C, et al. respiratory distress syndrome in preterm infants of less than 32 weeks: what difference does giving 100 or 200 mg/kg of exogenous surfactant make? Pediatr Pulmonol. 2022 May 16; 57(9): 2067–73.
9. Trembath A, Hornik CP, Clark R, Smith PB, Daniels J, Laughon M, et al. Comparative effectiveness of surfactant preparations in premature infants. J Pediatr. 2013;163:955–60. E951.
10. Ramanathan R, Bhatia JJ, Sekar K, Ernst FR. Mortality in preterm infants with respiratory distress syndrome treated with poractant alfa, calfactant or beractant: a retrospective study. J Perinatol. 2013;33:119–25.
11. Paul S, Rao S, Kohan R, McMichael J, French N, Zhang G, et al. Poractant alfa versus beractant for respiratory distress syndrome in preterm infants: a retrospective cohort study. J Paediatr Child Health. 2013;49:839–44.
12. Naseh A, Yekta BG. INSURE method (INtubation-SURfactant- Extubation) in early and late premature neonates with respiratory distress: factors affecting the outcome and survival rate. Turk J Pediatr. 2014;56:232–7.
13. Goss KCW, Gale C, Malone R, Longford N, Ratcliffe K, Modi N. Effect of surfactant dose on outcomes

in preterm infants with respiratory distress syndrome: the OPTI-SURF study protocol. BMJ Open 2020;10:e038959.
14. Magni T, Ragni C, Pelizzi N, Sharma S, Perez-Kempner L, Turkstra E et al. Health Economic Studies of Surfactant Replacement Therapy in Neonates with Respiratory Distress Syndrome: A Systematic Literature Review. Pharmacoecon Open. 2023 May;7(3):359-371.
15. Mussavi M, Mirnia K, Asadollahi K. Comparison of the efficacy of three natural surfactants (Curosurf, Survanta, and Alveofact) in the treatment of respiratory distress syndrome among neonates: a randomized controlled trial. Iran J Pediatr. 2016;26: e5743.
16. Najafian B, Karimi-Sari H, Khosravi MH, Nikjoo N, Amin S, Shohrati M. Comparison of efficacy and safety of two available natural surfactants in Iran, Curosurf and Survanta in treatment of neonatal respiratory distress syndrome: a randomized clinical trial. Contemp Clin Trials Commun. 2016; 3:55–9.
17. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-world evidence—what is it and what can it tell us? N Engl J Med. 2016; 375:2293–7.
18. Thébaud B, Goss KN, Laughon M, Whitsett JA, Abman SH, Steinhorn RH*et al.* Bronchopulmonary dysplasia. *Nat Rev Dis Primers*2019; 5, 78
19. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967 Feb 16;276(7):357-68.
20. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics. 1988 Oct;82(4):527-32.
21. Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics 2004; 114, 1305–1311
22. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV et al. Bronchopulmonary dysplasia: executive summary of a workshop. J. Pediatr. 2018; 197, 300–308
23. Isayama T, Lee SK, Yang J, Lee D, Daspal S, Dunn M et al. Revisiting the definition of bronchopulmonary dysplasia: effect of changing panoply of respiratory support for preterm neonates. JAMA Pediatr. 2017; 171, 271–279.
24. Svedenkrans J, Stoecklin B, Jones JG, Doherty DA, Pillow JJ. Physiology and Predictors of Impaired Gas Exchange in Infants with Bronchopulmonary Dysplasia. Am J Respir Crit Care Med. 2019 Aug 15;200(4):471-480.
25. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants: an evidence- based approach. Am. J. Respir. Crit. Care Med. 2019; 200, 751–759.

Hosted file

`Tables.docx` available at https://authorea.com/users/475664/articles/648875-comparison-of-porcine-versus-bovine-surfactant-in-preterm-respiratory-distress-syndrome-evidence-from-real-world-data-a-multicenter-collaboration-from-karnataka