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Assess impact of Nebulized surfactant to lessen respiratory distress severity

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Abstract
Background: Neonatal respiratory distress syndrome (RDS) is commonly managed with non-invasive nasal continuous positive airway pressure (nCPAP). However, some infants experience nCPAP failure, necessitating intubation and surfactant administration. While bolus surfactant delivery is effective, it carries risks. Nebulised surfactant offers a non-invasive alternative, but its efficacy in reducing nCPAP failure in preterm neonates remains unclear.
Methods: This trial evaluated the safety and effectiveness of nebulised surfactant for preterm neonates (290–336 weeks gestational age) with mild-to-moderate RDS on nCPAP. Eligible neonates were randomized within 4 hours of birth to receive nebulised surfactant (200 mg/kg poractant alfa) or sham nebulisation. Primary outcomes included the need for intubation within 72 hours and mean duration of mechanical ventilation. Secondary outcomes included neonatal morbidities and physiological stability. Data analysis followed an intention-to-treat approach.
Results: Of 64 enrolled infants, the nebulised surfactant group had a significantly lower intubation rate within 72 hours compared to controls (RR = 0.526, 95% CI 0.292–0.950). The reduction was most pronounced in infants aged 320–336 weeks' gestation. The median duration of mechanical ventilation did not differ significantly between groups. Safety analysis revealed no severe adverse effects, with transient hypercapnia during nebulisation resolving immediately. Neonatal complications were comparable between groups.
Conclusion: Nebulised surfactant reduces nCPAP failure rates in preterm infants with mild RDS, particularly in older gestational subgroups, without increasing adverse outcomes. Larger trials are necessary to confirm these findings and explore alternative delivery methods and interfaces.

Introduction

The use of non-invasive nasal continuous positive airway pressure (nCPAP) as an initial intervention for neonatal respiratory distress syndrome (RDS) is becoming more prevalent. Nevertheless, in some cases, the progression of RDS may necessitate delayed intubation followed by surfactant administration via bolus therapy. Postponing surfactant delivery can lead to alveolar collapse and subsequent atelectrauma, which may intensify respiratory complications and extend the need for mechanical ventilation (1–4). Although administering surfactant via brief tracheal instrumentation could mitigate atelectrauma, this approach carries potential risks, including improper tube placement, tracheal injury, transient cardiovascular instability, stress responses, and the need for temporary sedation or paralysis (5–8).

Nebulisation of surfactant offers a non-invasive alternative that aligns with less invasive treatment strategies (9, 10). In animal studies, nebulised surfactant has demonstrated benefits, including fewer adverse haemodynamic effects compared to bolus instillation, improved distribution uniformity, enhanced lung compliance, better ventilation

efficiency, and improved oxygenation (7, 11, 12, 13). The use of aerosolised surfactant for unventilated neonates with RDS was first reported in 1964, employing a method where the aerosol was delivered within an incubator (14). Subsequent investigations predominantly utilized jet nebulisation (15–18), a method with low efficiency due to air entrainment (19). Of these, only one study used a randomised controlled trial design, showing no significant impact of nebulised surfactant on ventilation requirements, nCPAP duration, oxygen needs, or bronchopulmonary dysplasia rates (16). A Cochrane review in 2012 highlighted the lack of sufficient evidence from randomised trials to recommend nebulised surfactant for preterm infants at risk of RDS (20).

Recent advancements, such as miniature vibrating membrane nebulisers, have improved delivery efficiency compared to jet nebulisers by minimizing surfactant loss (21). Despite these advancements, delivery efficiency remains lower with nebulisation via nasal prongs or masks compared to tracheal intubation (22). Preliminary data from a non-randomised pilot study using a vibrating membrane nebuliser indicated reduced rates of nCPAP failure and lower need for bolus surfactant therapy in preterm infants, compared to historical controls (18). While promising, the non-randomised design limits conclusions about the effectiveness of nebulised surfactant in managing neonatal RDS.

This study aimed to assess the clinical effectiveness and practicality of nebulised surfactant in treating RDS in very preterm neonates. The hypothesis tested was that early administration of nebulised surfactant, within the first four hours of life, to neonates with signs of RDS would decrease the incidence of nCPAP failure without increasing the occurrence of adverse outcomes.

Methods

Thisstudy was conducted to evaluate the feasibility, safety, and short-term efficacy of nebulized surfactant for treating developing RDS in infants born at 290–336 weeks of gestational age (GA).

Newborns were recruited by a designated team (SM, CAB) over a specified timeframe. The inclusion criteria required neonates to be between 290–336 weeks of GA, less than four hours old, and showing mild to moderate RDS signs necessitating treatment with nCPAP at pressures between 5–8 cmH2O and supplemental oxygen (FiO2) levels of 0.22–0.30 to maintain peripheral oxyhaemoglobin saturation between 86% and 94%. Exclusion criteria included prior intubation or surfactant administration, pneumothorax, unstable cardiorespiratory status, cardiothoracic malformations, and identifiable chromosomal abnormalities.

The intervention group received an aerosolized surfactant dose of 200 mg/kg body weight (poractant alfa, Chiesi Farmaceutici SpA) using a customized vibrating membrane nebulizer (eFlow neonatal nebulizer system, PARI Pharma). Nebulization was initiated promptly after randomization. If respiratory distress persisted (tachypnea >60 breaths/min, muscle retractions, or grunting) or oxygen requirements remained elevated after 12 hours, a second dose of 100 mg/kg was administered.

Infants who failed nCPAP were intubated and given surfactant as per standard unit practice (200 mg/kg initially, with a repeat dose of 100 mg/kg after 12 hours if required). Extubation criteria were not specified.

The primary outcomes assessed were the need for intubation within the first 72 hours of life (dichotomous) and the mean duration of mechanical ventilation at 72 hours (continuous). Secondary outcomes included the proportion of infants still intubated at 24 hours, 72 hours, and 7 days; time to intubation; total surfactant dosage; associated neonatal morbidities; and physiological stability after randomization.

Statistical Methods

Analysis was conducted on an intention-to-treat basis for the full cohort and predefined GA strata. Dichotomous outcomes were analyzed using Pearson's χ^2 test and relative risk (RR), with Fisher's exact test for low-event rates. Continuous outcomes were summarized using means (SD) or medians (range), depending on distribution, and compared using t-tests or Mann-Whitney U tests. Kaplan-Meier survival analysis with the log-rank (Mantel-Cox) χ^2 test was employed for time-dependent outcomes. Reported p-values were two-sided.

Results

Over a study period 64 infants participated in the trial. One infant did not receive a second nebulised surfactant dose despite ongoing oxygen supplementation, constituting a protocol deviation. Another was intubated immediately after randomisation, prior to receiving nebulised surfactant. Both were included in the final analysis based on the intention-to-treat principle. Recruitment ceased prematurely due to limited funding and staffing resources.

Of the 360 infants initially eligible, only 64 were enrolled, primarily because study staff were unavailable to maintain blinding during interventions. No notable differences were found in the demographic or clinical profiles of the enrolled infants (Table 1). However, the proportion of male infants and cesarean deliveries was higher among the

recruited group compared to eligible but non-enrolled infants, although no evidence of systematic selection bias was observed.

The use of nebulised surfactant significantly decreased the need for intubation within the first 72 hours. Intubation was required for 11 of 32 infants in the intervention group compared to 22 of 32 in the nCPAP-only group (RR=0.526, 95% CI 0.292 to 0.950). This benefit was most pronounced in the subgroup of infants aged 320–336 weeks' gestation, where 1 of 11 infants in the nebulisation group was intubated compared to 10 of 13 in the control group (RR=0.254, 95% CI 0.089 to 0.727). In contrast, there was no difference in intubation rates among infants born at 290–316 weeks' gestation (RR=0.860, 95% CI 0.389 to 1.90).

The median duration of mechanical ventilation over the first 72 hours did not differ significantly between groups: 0 hours (range 0–62) in the nebulised surfactant group versus 9 hours (range 0–64) in the control group (p=0.220).No significant differences were observed between the two groups in the total duration of mechanical respiratory support or supplemental oxygen use. The proportion of infants remaining intubated at 24 hours, 72 hours, or 7 days was also comparable.

Among infants who required intubation due to nCPAP failure, those in the nebulised surfactant group had a slightly longer duration of ventilation. However, this difference was influenced by gestational age differences between the groups. In the subgroup of 290–316 weeks' gestation infants, the median ventilation duration was not significantly different: 25.5 hours (IQR 13.9–82) for the nebulised group versus 19.2 hours (IQR 13.6–46.7) for the control group (U=58.0, p=0.436).

The total dose of surfactant administered was similar across groups. Nine infants received a second dose of nebulised surfactant after 12 hours due to persistent oxygen needs or respiratory distress. The mean difference in post-intubation bolus surfactant use was 9.2 mg/kg (95% CI −14.5 to 32.9) between groups.

Among infants who experienced nCPAP failure, the time to meet failure criteria was significantly longer in the nebulised surfactant group .The median delay in time to intubation was 4.5 hours (95% CI −0.18 to 7.17) compared to the control group. Infants at 290–316 weeks' gestation in the nebulised group tended to show a prolonged response to nCPAP, though the difference was not statistically significant.

During nebulisation, some infants exhibited transient increases in transcutaneous carbon dioxide levels (TcpCO2), which resolved immediately after removing the face mask. One infant experienced an apnoea episode, requiring a brief interruption of the procedure. No significant changes in heart rate or oxygen desaturation were noted during nebulisation.

The incidence of neonatal complications was similar between groups. Two control group infants developed pneumothorax. The most common reasons for nCPAP failure included exceeding the maximum allowable FiO2 and clinician assessment of severe respiratory distress (Tables 3 and 4). Indicators of respiratory distress were consistent between groups among infants who required intubation.

Table 1.Patient demographics

	Control (n=32)	Nebulised surfactant (n=32)	P values
Gestation (weeks)	31.4 (1.4)	31.4 (1.4)	0.841
Birth weight (g)	1645 (409)	1562 (399)	0.415
Birth weight Z score[31]	0.00 (0.81)	−0.29 (0.69)	0.129
Male, n (%)	26 (81.3)	22 (68.8)	0.387
Antenatal steroids			
Any steroids, n (%)	29 (90.6)	31 (96.9)	0.613
Complete course, n(%)	16 (50.0)	21 (65.6)	0.311
Caesarean section, n (%)	23 (71.9)	26 (81.3)	0.556
Apgar 1 min	7 (2)	7 (2)	0.791
Apgar 5 min	8 (1)	8 (1)	0.706
Age at first nebulisation (min)	–	178 (52)	–

Values are mean (SD).

Discussion

This study aimed to assess the effectiveness of nebulized surfactant administered within the first four hours of life for managing respiratory distress syndrome (RDS) in preterm neonates using a non-invasive approach. The combination of nebulized surfactant and nasal continuous positive airway pressure (nCPAP) aligns with recent advances in neonatal respiratory care. The findings, indicating a reduced need for intubation with the use of a vibrating membrane nebulizer, contrast with a prior trial that employed a jet nebulizer system (16). The vibrating

membrane nebulizer offers enhanced surfactant delivery efficiency without issues such as protein denaturation or aerosol dilution seen in other systems (9, 23). This device requires only a patent airway maintained through face mask nCPAP, is highly portable, and can operate independently of gas flow, making it feasible for use even outside tertiary care settings.

The study confirmed the safety of nebulized surfactant when appropriate monitoring is in place. Apnea requiring a temporary cessation of nebulization was rare (1 of 32 cases), and increases in TcpCO2 linked to external dead space were transient. Additionally, there were no significant differences in adverse clinical outcomes between groups within the first week of life, suggesting minimal side effects.

Subgroup analysis revealed that the intervention was more effective in reducing intubation in moderately preterm infants. In the 32–33 weeks' gestational age (GA) group, most control group infants required intubation for impaired oxygenation or ventilation, while the treated group showed improved outcomes, potentially due to a lung recruitment effect. These subgroup findings, however, warrant confirmation in larger, adequately powered trials, as this study was not designed to detect subgroup-specific outcomes.

For infants who eventually required intubation, the nebulized surfactant group reached failure criteria later than controls, suggesting a physiological benefit. Notably, the time to failure in the nebulized group was close to 12 hours, implying that surfactant redosing might be necessary before this time point. However, the duration of mechanical ventilation and extubation outcomes did not differ significantly between groups, with potential confounders including variability in extubation criteria and differences in the maturity of the infants.

The observed nCPAP failure rate was higher than anticipated, possibly due to delays in recruitment or a bias towards early bolus surfactant administration by blinded clinicians, even when oxygenation levels were not severely compromised. This bias was particularly evident in the less mature infant group, highlighting the need for a more standardized approach in future studies.

Despite these limitations, the study offers valuable insights into the potential of nebulized surfactant. Future research should target a more consistent oxygenation impairment index (e.g., nCPAP pressure × FiO2) and consider evaluating nebulization interfaces, such as supraglottic masks, which may enhance delivery efficiency but require further investigation (24–27). Moreover, optimization of the nebulizer membrane design is necessary to ensure efficacy in extremely preterm infants and across different delivery interfaces (30).

In conclusion, early administration of nebulized surfactant may support non-invasive respiratory management in preterm infants with mild RDS. To validate these findings, further randomized controlled trials are essential, focusing on larger sample sizes, different patient interfaces, and comparisons with contemporary less-invasive surfactant delivery techniques.

References

1. Dani C, Bertini G, Pezzati M, et al. . Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. Pediatrics 2004;113:e560–3. 10.1542/peds.113.6.e560

2. Dargaville PA, Aiyappan A, Cornelius A, et al. . Preliminary evaluation of a new technique of minimally invasive surfactant therapy. Arch Dis Child Fetal Neonatal Ed 2011;96:F243–8. 10.1136/adc.2010.192518

3. Göpel W, Kribs A, Ziegler A, et al. . Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet 2011;378:1627–34. 10.1016/S0140-6736(11)60986-0

4. Reininger A, Khalak R, Kendig JW, et al. . Surfactant administration by transient intubation in infants 29 to 35 weeks' gestation with respiratory distress syndrome decreases the likelihood of later mechanical ventilation: a randomized controlled trial. J Perinatol 2005;25:703–8. 10.1038/sj.jp.7211381

5. Newman B, Oh KS, Ks O. Iatrogenic tracheobronchial perforation in infants. J Thorac Imaging 1994;9:269–72.

6. Marshall TA, Deeder R, Pai S, et al. . Physiologic changes associated with endotracheal intubation in preterm infants. Crit Care Med 1984;12:501–3.

7. Dijk PH, Heikamp A, Bambang Oetomo S. Surfactant nebulisation prevents the adverse effects of surfactant therapy on blood pressure and cerebral blood flow in rabbits with severe respiratory failure. Intensive Care Med 1997;23:1077–81.

8. Verder H, Robertson B, Greisen G, et al. . Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. N Engl J Med 1994;331:1051–5. 10.1056/NEJM199410203311603

9. Pillow JJ, Minocchieri S. Innovation in surfactant therapy II: surfactant administration by aerosolization. Neonatology 2012;101:337–44. 10.1159/000337354

10. Herting E. Less invasive surfactant administration (LISA) - ways to deliver surfactant in spontaneously breathing infants. Early Hum Dev 2013;89:875–80. 10.1016/j.earlhumdev.2013.08.023
11. Schermuly RT, Günther A, Weissmann N, et al. . Differential impact of ultrasonically nebulized versus tracheal-instilled surfactant on ventilation-perfusion (VA/Q) mismatch in a model of acute lung injury. Am J Respir Crit Care Med 2000;161:152–9. 10.1164/ajrccm.161.1.9812017
12. Wagner MH, Amthauer H, Sonntag J, et al. . Endotracheal surfactant atomization: an alternative to bolus instillation? Crit Care Med 2000;28:2540–4.
13. Lewis JF, Ikegami M, Jobe AH, et al. . Aerosolized surfactant treatment of preterm lambs. J Appl Physiol 1991;70:869–76. 10.1152/jappl.1991.70.2.869
14. Robillard E, Alarie Y, Dagenais-Perusse P, et al. . Microaerosol administration of synthetic beta-gamma-dipalmitoyl-l-alpha-lecithin in the respiratory distress syndome: a preliminary report. Can Med Assoc J 1964;90:55–7.
15. Arroe M, Pedersen-Bjergaard L, Albertsen P, et al. . Inhalation of aerosolized surfactant (Exosurf) to neonates treated with nasal continuous positive ariway pressure. Prenat Neonat Med 1998;1998:346–52.
16. Berggren E, Liljedahl M, Winbladh B, et al. . Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. Acta Paediatr 2000;89:460–4.
17. Jorch G, Hartl H, Roth B, et al. . Surfactant aerosol treatment of respiratory distress syndrome in spontaneously breathing premature infants. Pediatr Pulmonol 1997;24:222–4.
18. Finer NN, Merritt TA, Bernstein G, et al. . An open label, pilot study of Aerosurf® combined with nCPAP to prevent RDS in preterm neonates. J Aerosol Med Pulm Drug Deliv 2010;23:303–9. 10.1089/jamp.2009.0758
19. Collis GG, Cole CH, Le Souëf PN. Dilution of nebulised aerosols by air entrainment in children. Lancet 1990;336:341–3.
20. Abdel-Latif ME, Osborn DA. Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database Syst Rev 2012;10:CD008310 10.1002/14651858.CD008310.pub2
21. Tiemersma S, Minocchieri S, van Lingen RA, et al. . Vibrating membrane devices deliver aerosols more efficient than standard devices: a study in a neonatal upper airway model. J Aerosol Med Pulm Drug Deliv 2013;26:280–6. 10.1089/jamp.2012.0993
22. Linner R, Perez-de-Sa V, Cunha-Goncalves D. Lung deposition of nebulized surfactant in newborn piglets. Neonatology 2015;107:277–82. 10.1159/000369955
23. Wagner MH, Wiethoff S, Friedrich W, et al. . Ultrasonic surfactant nebulization with different exciting frequencies. Biophys Chem 2000;84:35–43.
24. Trevisanuto D, Grazzina N, Ferrarese P, et al. . Laryngeal mask airway used as a delivery conduit for the administration of surfactant to preterm infants with respiratory distress syndrome. Biol Neonate 2005;87:217–20. 10.1159/000083370
25. Pinheiro JM, Santana-Rivas Q, Pezzano C. Randomized trial of laryngeal mask airway versus endotracheal intubation for surfactant delivery. J Perinatol 2016;36:196–201. 10.1038/jp.2015.177
26. Roberts KD, Brown R, Lampland AL, et al. . Laryngeal mask airway for surfactant administration in neonates: a randomized, controlled trial. J Pediatr 2018;193:40–6. 10.1016/j.jpeds.2017.09.068
27. Wanous AA, Wey A, Rudser KD, et al. . Feasibility of laryngeal mask airway device placement in neonates. Neonatology 2017;111:222–7. 10.1159/000450691
28. Barbosa RF, Marcatto JO, Silva AC, et al. . ProSealTM laryngeal mask airway for surfactant administration in the treatment of respiratory distress syndrome in a premature infant. Rev Bras Ter Intensiva 2012;24:207–10.
29. Barbosa RF, Simões e Silva AC, Silva YP. A randomized controlled trial of the laryngeal mask airway for surfactant administration in neonates. J Pediatr 2017;93:343–50. 10.1016/j.jped.2016.08.007
30. Minocchieri S, Burren JM, Bachmann MA, et al. . Development of the premature infant nose throat-model (PrINT-Model): an upper airway replica of a premature neonate for the study of aerosol delivery. Pediatr Res 2008;64:141–6. 10.1203/PDR.0b013e318175dcfa
31. Fenton TR, Kim JH Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59 10.1186/1471-2431-13-59