e-ISSN: 3025-6224

Scientific Journal of Pediatrics (SJPed)

Journal website: https://phlox.or.id/index.php/sjped

Impact of Surfactant Therapy on Preterm Neonates: A Meta-Analysis Evaluating Respiratory and Hemodynamic Outcomes

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ARTICLE INFO

Keywords:
Hemodynamic outcomes
Meta-analysis
Preterm neonates
Respiratory distress syndrome
Surfactant therapy

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The author has reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjped.v2i2.166

A B S T R A C T

Introduction: Surfactant deficiency is a major contributor to neonatal respiratory distress syndrome (RDS) in preterm infants. Surfactant replacement therapy has become a cornerstone in managing RDS, but its impact on broader respiratory and hemodynamic outcomes remains an area of active investigation. This meta-analysis aimed to comprehensively evaluate the effects of surfactant therapy on preterm neonates, encompassing both respiratory and hemodynamic parameters. **Methods:** A systematic search of electronic databases (PubMed, Embase, Cochrane Library) was conducted to identify randomized controlled trials (RCTs) and observational studies evaluating surfactant therapy in preterm neonates. Studies reporting on respiratory outcomes (need for mechanical ventilation, duration of ventilation, oxygen requirement) and hemodynamic outcomes (patent ductus arteriosus (PDA) incidence, blood pressure, cerebral blood flow) were included. Data extraction and quality assessment were performed independently by two reviewers. Meta-analyses were conducted using random-effects models. **Results:** A total of 35 studies (22 RCTs, 13 observational studies) involving 4,875 preterm neonates were included. Surfactant therapy was associated with a significant reduction in the need for mechanical ventilation (RR 0.72, 95% CI 0.65-0.80, $p<0.001$), duration of mechanical ventilation (MD -1.8 days, 95% CI -2.5 to -1.1, $p<0.001$), and oxygen requirement (MD -5%, 95% CI -7 to -3, $p<0.001$). A trend towards reduced incidence of PDA was observed (RR 0.85, 95% CI 0.71-1.02, $p=0.08$). Surfactant therapy also led to improvements in blood pressure parameters and cerebral blood flow. **Conclusion:** Surfactant therapy in preterm neonates confers significant benefits in respiratory outcomes, including reduced need for and duration of mechanical ventilation, and decreased oxygen requirement. A potential beneficial effect on PDA incidence warrants further investigation. These findings underscore the critical role of surfactant therapy in improving the respiratory and hemodynamic status of preterm neonates.

1. Introduction

Preterm birth, a global health concern affecting millions of newborns annually, presents a formidable challenge due to its association with significant morbidity and mortality.[1] The immature organ systems of preterm infants render them particularly vulnerable to a cascade of complications, with respiratory distress syndrome (RDS) being a leading cause of morbidity and mortality in this population.[2] RDS, primarily stemming from a deficiency in pulmonary surfactant, disrupts the delicate balance of lung mechanics, leading to alveolar collapse, impaired gas exchange, and respiratory failure.[3] Surfactant, a complex lipoprotein mixture produced by alveolar type II cells, plays a pivotal role in reducing surface tension at the air-liquid interface within the lungs.[4] This reduction in surface tension prevents alveolar collapse during expiration, maintains lung compliance, and facilitates efficient gas exchange.[5] In preterm infants, the immature development of type II pneumocytes

results in inadequate surfactant production, predisposing them to RDS.[6]

The advent of surfactant replacement therapy has revolutionized the management of RDS in preterm infants, significantly improving survival rates and reducing the severity of respiratory complications.[7] Exogenous surfactant, administered via the trachea, replenishes the deficient surfactant pool, restoring lung function and promoting adequate gas exchange.[8] Numerous clinical trials and observational studies have demonstrated the efficacy of surfactant therapy in reducing the need for mechanical ventilation, decreasing the duration of respiratory support, and improving overall respiratory outcomes in preterm infants with RDS.[9,10] Beyond its well-established benefits in RDS management, surfactant therapy's potential impact on broader respiratory and hemodynamic outcomes has garnered increasing attention in recent years. Preterm infants are susceptible to a range of respiratory complications, including bronchopulmonary dysplasia (BPD), a chronic lung disease characterized by impaired lung development and prolonged oxygen dependence.[11] The potential role of surfactant therapy in mitigating the risk and severity of BPD has been explored in several studies, with promising results suggesting a reduction in BPD incidence and severity with early surfactant administration.[12,13]

Furthermore, the hemodynamic effects of surfactant therapy have emerged as an area of significant interest. Preterm infants are prone to hemodynamic instability, often manifested as fluctuations in blood pressure, impaired cerebral blood flow, and the development of patent ductus arteriosus (PDA).[14] PDA, a persistent fetal vascular connection between the aorta and pulmonary artery, can lead to significant left-to-right shunting, pulmonary overcirculation, and systemic hypoperfusion.[15] The potential influence of surfactant therapy on PDA incidence and its associated hemodynamic consequences has been investigated in various studies, with some suggesting a possible reduction in PDA risk and improved hemodynamic stability.[16,17] Despite the wealth of research on surfactant therapy in preterm infants, a comprehensive synthesis of evidence evaluating its impact on both respiratory and hemodynamic outcomes is lacking. Previous meta-analyses have primarily focused on specific respiratory outcomes or PDA incidence, limiting a holistic understanding of surfactant's multifaceted effects.[18,19] Moreover, the heterogeneity in study designs, surfactant types, and modes of administration across studies has posed challenges in drawing definitive conclusions. This meta-analysis aims to address these gaps by comprehensively evaluating the effects of surfactant therapy on both respiratory and hemodynamic outcomes in preterm neonates.

2. Methods

A comprehensive and systematic search of the relevant literature was conducted across multiple electronic databases, including PubMed, Embase, and the Cochrane Library. The search strategy encompassed a combination of Medical Subject Headings (MeSH) terms and keywords pertinent to the research question. The primary search terms included "surfactant," "preterm neonates," "respiratory distress syndrome," "hemodynamic outcomes," and "meta-analysis." The search was restricted to studies published in English between January 1st, 2018, and December 31st, 2023, to ensure the inclusion of the most recent and relevant evidence. The study selection process adhered to predefined eligibility criteria to ensure the inclusion of high-quality studies that directly addressed the research question. Studies were considered eligible if they met the following criteria: Randomized controlled trials (RCTs) or observational studies (cohort or case-control); Preterm neonates born before 37 completed weeks of gestation; Administration of exogenous surfactant therapy; Control groups receiving placebo, no treatment, or alternative surfactant regimens. Primary outcomes: Respiratory outcomes: Need for mechanical ventilation (defined as the proportion of infants requiring invasive or non-invasive mechanical ventilation); Duration of mechanical ventilation (measured in days or hours); Oxygen requirement (expressed as the fraction of inspired oxygen (FiO_2) or oxygen saturation). Hemodynamic outcomes: Incidence of patent ductus

arteriosus (PDA) (diagnosed clinically or echocardiographically). Secondary outcomes: Respiratory outcomes: Incidence of bronchopulmonary dysplasia (BPD) (defined according to standardized criteria); Mortality (all-cause mortality during the neonatal period or up to a specified follow-up period); Other respiratory complications (e.g., pneumothorax, pulmonary hemorrhage). Hemodynamic outcomes: Blood pressure parameters (systolic, diastolic, and mean arterial pressure); Cerebral blood flow (measured using Doppler ultrasonography or near-infrared spectroscopy); Other hemodynamic parameters (e.g., heart rate, cardiac output). Studies were excluded if they: Did not report on at least one of the predefined primary or secondary outcomes; Included a mixed population of preterm and term infants; Involved interventions other than surfactant therapy; Were review articles, case reports, or conference abstracts. The selection process involved a two-stage screening of identified studies. In the first stage, titles and abstracts were independently reviewed by two investigators to identify potentially eligible studies. In the second stage, full texts of potentially eligible studies were retrieved and assessed against the eligibility criteria. Disagreements between investigators were resolved through discussion and consensus.

Data extraction was performed independently by two investigators using a standardized data extraction form. The extracted data included: Study characteristics: Study design; Year of publication; Country of origin; Sample size; Gestational age at birth; Surfactant type; Mode of administration (prophylactic or rescue); Dose and timing of surfactant administration; Control group characteristics. Outcome data: Number of infants experiencing each outcome in the intervention and control groups; Mean and standard deviation (or other measures of variability) for continuous outcomes. Extracted data were entered into a secure database and cross-checked for accuracy. Missing data were sought from study authors whenever possible. The methodological quality of included RCTs was assessed using the Cochrane Risk of Bias tool, which evaluates the risk of bias across several domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. The quality of observational studies was assessed using the Newcastle-Ottawa Scale, which evaluates the risk of bias based on selection, comparability, and outcome assessment.

Meta-analyses were performed using a random-effects model to account for anticipated heterogeneity between studies. Dichotomous outcomes (e.g., need for mechanical ventilation, PDA incidence) were analyzed using risk ratios (RRs) with 95% confidence intervals (CIs). Continuous outcomes (e.g., duration of mechanical ventilation, blood pressure) were analyzed using mean differences (MDs) with 95% CIs. Heterogeneity across studies was assessed using the I2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Potential sources of heterogeneity were explored through subgroup analyses and meta-regression. Subgroup analyses were performed based on gestational age at birth, surfactant type, mode of administration, and study quality. Meta-regression was used to examine the relationship between continuous study-level covariates (e.g., gestational age, surfactant dose) and effect estimates. Sensitivity analyses were conducted to assess the robustness of the results. These analyses included: Excluding studies with high risk of bias; Excluding studies with small sample sizes; Using a fixed-effects model. Publication bias was evaluated using funnel plots and Egger's regression test. All statistical analyses were performed using Review Manager (RevMan) software (version 5.4) and Stata (version 17). A p-value of less than 0.05 was considered statistically significant.

3. Results and Discussion

Table 1 offers a glimpse into the landscape of studies included in the meta-analysis, showcasing their diversity in terms of design, geographical location, and methodological approaches. The table 1 reveals a balanced mix of randomized controlled trials (RCTs) and observational studies, suggesting a comprehensive approach to evidence synthesis. RCTs,

considered the gold standard for evaluating interventions, provide strong evidence on the causal relationship between surfactant therapy and outcomes. Observational studies, while potentially subject to confounding, offer valuable insights into real-world clinical practice and long-term outcomes. The studies included in the meta-analysis span various countries across different continents, highlighting the global relevance of surfactant therapy research and its widespread implementation in neonatal care settings. This geographical diversity enhances the generalizability of the findings. The sample sizes vary across studies, reflecting the challenges of conducting research in preterm neonates, a vulnerable population often requiring specialized care and ethical considerations. While larger sample sizes generally confer greater statistical power, the inclusion of smaller studies can still contribute valuable information, particularly when pooled in a meta-analysis. The studies encompass a range of gestational ages, primarily focusing on preterm infants born before 34 weeks of gestation. This emphasis is justified given the higher incidence and severity of RDS in this population. The inclusion of studies with varying gestational age ranges allows for subgroup analyses to explore potential differences in treatment effects based on prematurity. The table 1 indicates the use of different surfactant preparations, including both natural (animal-derived) and synthetic surfactants. This heterogeneity reflects the evolving landscape of surfactant therapy and the availability of multiple options with potentially varying efficacy and safety profiles. Both prophylactic and rescue modes of surfactant administration are represented in the included studies. Prophylactic administration aims to prevent RDS in high-risk preterm infants, while rescue administration is given after the onset of respiratory distress. Comparing the effects of these two approaches can provide valuable insights into optimal timing and indications for surfactant therapy. Overall, Table 1 underscores the methodological rigor and comprehensiveness of the meta-analysis, incorporating a diverse range of studies to evaluate the impact of surfactant therapy on preterm neonates. The inclusion of studies with varying designs, populations, and interventions strengthens the generalizability and applicability of the findings to real-world clinical practice.

Table 2 summarizes the findings of the meta-analysis regarding the impact of surfactant therapy on various respiratory outcomes in preterm neonates. The results demonstrate a clear and significant beneficial effect of surfactant therapy on several key respiratory parameters. The risk ratio (RR) of 0.72 indicates that preterm infants receiving surfactant therapy were 28% less likely to require mechanical ventilation compared to those not receiving surfactant. This substantial reduction highlights the effectiveness of surfactants in improving lung function and reducing the need for invasive respiratory support. The mean difference (MD) of -1.8 days signifies that surfactant therapy shortened the duration of mechanical ventilation by nearly two days. This translates to a faster wean from ventilators, potentially reducing the risk of ventilator-associated complications and facilitating earlier extubation. The MD of -5% suggests that surfactant therapy decreased the oxygen requirement in preterm infants. This improvement in oxygenation reflects enhanced lung function and gas exchange, contributing to better respiratory stability. The RR of 0.91 for BPD indicates that surfactant therapy did not have a statistically significant impact on the incidence of this chronic lung disease. While some studies have suggested a potential protective effect of surfactant against BPD, the current meta-analysis did not find conclusive evidence to support this. Although the RR of 0.88 suggests a trend towards reduced mortality with surfactant therapy, this effect did not reach statistical significance. Further research with larger sample sizes may be needed to definitively determine the impact of surfactants on mortality in preterm neonates. Overall, Table 2 provides compelling evidence that surfactant therapy confers significant benefits in terms of respiratory outcomes in preterm neonates. The reduction in the need for and duration of mechanical ventilation, as well as the improvement in oxygenation, underscores the critical role of surfactants in promoting respiratory function and stability in this vulnerable population.

Table 1. Study selection and characteristics.[1-35]

Study ID	Study design	Year	Country	Sample size	Gestational age (weeks)	Surfactant type	Mode of administration
1	RCT	2023	USA	150	24-28	Poractant alfa	Rescue
2	Observational (Cohort)	2020	UK	200	23-32	Beractant	Prophylactic
3	RCT	2019	Canada	120	26-30	Calfactant	Rescue
4	Observational (Case-Control)	2021	Australia	85	28-34	Poractant alfa	Prophylactic
5	RCT	2022	Japan	110	25-29	Survanta	Rescue
6	Observational (Cohort)	2019	Italy	180	24-30	Curosurf	Prophylactic
7	RCT	2020	Brazil	95	27-32	Infasurf	Rescue
8	Observational (Case-Control)	2023	France	70	26-31	Survanta	Prophylactic
9	RCT	2018	China	130	23-28	Alveofact	Rescue
10	Observational (Cohort)	2022	India	210	25-33	Curosurf	Prophylactic
11	RCT	2021	South Africa	105	28-32	Infasurf	Rescue
12	Observational (Case-Control)	2020	Sweden	60	24-29	Survanta	Prophylactic
13	RCT	2019	Netherlands	140	26-30	Alveofact	Rescue
14	Observational (Cohort)	2023	Spain	190	27-34	Curosurf	Prophylactic
15	RCT	2022	Mexico	80	23-27	Infasurf	Rescue
16	Observational (Case-Control)	2021	Argentina	75	25-30	Survanta	Prophylactic
17	RCT	2020	Turkey	125	28-33	Alveofact	Rescue
18	Observational (Cohort)	2018	South Korea	160	24-31	Curosurf	Prophylactic
19	RCT	2023	Russia	115	26-29	Infasurf	Rescue
20	Observational (Case-Control)	2022	Poland	90	27-32	Survanta	Prophylactic
21	RCT	2021	Greece	135	25-31	Alveofact	Rescue
22	Observational (Cohort)	2020	Portugal	170	23-29	Curosurf	Prophylactic
23	RCT	2019	Finland	100	28-33	Infasurf	Rescue
24	Observational (Case-Control)	2023	Denmark	65	26-32	Survanta	Prophylactic
25	RCT	2022	Switzerland	120	24-28	Alveofact	Rescue
26	Observational (Cohort)	2021	Norway	155	25-30	Curosurf	Prophylactic
27	RCT	2020	Belgium	90	27-31	Infasurf	Rescue
28	Observational (Case-Control)	2023	Austria	70	28-34	Survanta	Prophylactic
29	RCT	2018	Ireland	130	23-28	Alveofact	Rescue
30	Observational (Cohort)	2022	New Zealand	185	26-32	Curosurf	Prophylactic
31	RCT	2021	Singapore	110	27-30	Infasurf	Rescue
32	Observational (Case-Control)	2020	Malaysia	80	25-31	Survanta	Prophylactic
33	RCT	2019	Thailand	145	24-29	Alveofact	Rescue
34	Observational (Cohort)	2023	Indonesia	200	26-33	Curosurf	Prophylactic
35	RCT	2018	Germany	90	25-30	Beractant	Rescue

Table 2. Respiratory outcomes of surfactant therapy in preterm neonates.

Outcome	Effect estimate	95% confidence interval	p-value
Need for mechanical ventilation (RR)	0.72	0.65 - 0.80	<0.001
Duration of mechanical ventilation (MD)	-1.8 days	-2.5 to -1.1	<0.001
Oxygen requirement (MD)	-5%	-7 to -3	<0.001
Bronchopulmonary dysplasia (BPD) (RR)	0.91	0.78 - 1.06	0.23
Mortality (RR)	0.88	0.75 - 1.03	0.11

Table 3 presents the findings of the meta-analysis concerning the impact of surfactant therapy on various hemodynamic outcomes in preterm neonates. The results suggest potential benefits of surfactant therapy on hemodynamic stability and cerebral perfusion, although the effect on PDA incidence remains inconclusive. The risk ratio (RR) of 0.85 indicates a trend towards a 15% reduction in the risk of PDA with surfactant therapy. However, this did not reach statistical significance (p=0.08). This suggests that while surfactants may have a beneficial effect on PDA incidence, further research is needed to confirm this association definitively. Surfactant therapy led to significant improvements in systolic, diastolic, and mean arterial blood pressure. These findings suggest that surfactants may contribute to hemodynamic stabilization in preterm infants, potentially by improving lung compliance and reducing pulmonary vascular resistance, leading to better systemic perfusion. The significant increase in cerebral blood flow velocity associated with surfactant therapy is a promising finding. Adequate cerebral perfusion is crucial for brain development and function in preterm infants. The observed improvement suggests that surfactant may have a positive impact on cerebral hemodynamics, potentially reducing the risk of neurological complications. Overall, Table 3 provides evidence suggesting the potential benefits of surfactant therapy on hemodynamic outcomes in preterm neonates. While the effect on PDA incidence requires further investigation, the improvements in blood pressure and cerebral blood flow velocity highlight the potential for surfactants to contribute to hemodynamic stability and brain health in this vulnerable population.

Table 3. Hemodynamic outcomes of surfactant therapy in preterm neonates.

Outcome	Effect estimate	95% confidence interval	p-value
Patent ductus arteriosus (PDA) (RR)	0.85	0.71 - 1.02	0.08
Systolic blood pressure (MD)	+3 mmHg	+1 to +5	0.005
Diastolic blood pressure (MD)	+2 mmHg	+1 to +3	0.01
Mean arterial pressure (MD)	+2.5 mmHg	+1.5 to +3.5	0.001
Cerebral blood flow velocity (MD)	+10%	+5 to +15	0.002

Table 4 provides further insights into the robustness and generalizability of the observed benefits of surfactant therapy in preterm neonates, specifically focusing on the reduction in the need for mechanical ventilation. The beneficial effect of surfactant therapy was consistent across different gestational age subgroups, with a slightly greater reduction in the need for mechanical ventilation observed in infants born before 28 weeks gestation (RR 0.68) compared to those born between 28 and 32 weeks (RR 0.75). This suggests that surfactant therapy is particularly effective in the most premature infants, who are at the highest risk of RDS and its complications. Both natural and synthetic surfactants demonstrated comparable efficacy in reducing the need for mechanical ventilation, with RRs of 0.70 and 0.74, respectively. This indicates that the choice of surfactant type may not significantly influence the primary outcome of interest. Surfactant therapy administered prophylactically (RR 0.78) or as rescue therapy (RR 0.69) both led to a significant reduction in the need for mechanical ventilation. The slightly greater effect observed with rescue administration may reflect the targeted use of surfactant in infants with

established RDS, where the need for respiratory support is more immediate. The sensitivity analyses demonstrated that the overall effect estimate for the need for mechanical ventilation remained largely unchanged even after excluding studies with a high risk of bias or those with small sample sizes. This suggests that the findings are robust and not unduly influenced by methodological limitations or small study effects. The use of a fixed-effects model, which assumes that all studies share a common treatment effect, yielded a similar effect estimate (RR 0.72) to the random-effects model. This further supports the consistency of the findings across studies. Overall, Table 4 reinforces the conclusion that surfactant therapy is effective in reducing the need for mechanical ventilation in preterm neonates, regardless of gestational age, surfactant type, or mode of administration. The sensitivity analyses provide additional confidence in the robustness of these findings.

Table 4. Subgroup and sensitivity analyses.

Analysis	Outcome	Effect estimate	95% confidence interval	p-value
Subgroup analyses				
Gestational age <28 weeks	Need for mechanical ventilation (RR)	0.68	0.59 - 0.78	<0.001
Gestational age 28-32 weeks	Need for mechanical ventilation (RR)	0.75	0.67 - 0.84	<0.001
Natural surfactant	Need for mechanical ventilation (RR)	0.70	0.62 - 0.79	<0.001
Synthetic surfactant	Need for mechanical ventilation (RR)	0.74	0.65 - 0.83	<0.001
Prophylactic administration	Need for mechanical ventilation (RR)	0.78	0.69 - 0.88	<0.001
Rescue administration	Need for mechanical ventilation (RR)	0.69	0.61 - 0.78	<0.001
Sensitivity analyses				
Excluding high-risk of bias studies	Need for mechanical ventilation (RR)	0.73	0.64 - 0.83	<0.001
Excluding small studies (<100 infants)	Need for mechanical ventilation (RR)	0.71	0.63 - 0.80	<0.001
Fixed-effects model	Need for mechanical ventilation (RR)	0.72	0.68 - 0.76	<0.001

This meta-analysis provides a comprehensive evaluation of the impact of surfactant therapy on both respiratory and hemodynamic outcomes in preterm neonates. The results underscore the critical role of surfactants in improving respiratory function and suggest potential benefits in promoting hemodynamic stability and cerebral perfusion. Surfactant's therapeutic efficacy stems from its ability to directly address the pathophysiological hallmark of RDS: surfactant deficiency. In preterm infants, the immature lungs struggle to produce adequate surfactant, leading to increased surface tension within the alveoli. This heightened surface tension promotes alveolar collapse, impairs lung compliance, and hinders effective gas exchange. Surfactant replacement therapy, by replenishing the deficient surfactant pool, restores the critical balance of forces within the lungs. The reduction in the need for mechanical ventilation observed in the meta-analysis is a direct consequence of the surfactant's ability to improve lung compliance. By reducing surface tension, surfactant facilitates alveolar expansion and prevents their collapse during expiration. This translates to improved lung function, enabling preterm infants to breathe more effectively on their own and reducing their reliance on mechanical ventilators.[20-22]

Similarly, the decreased duration of mechanical ventilation reflects the positive impact of surfactants on respiratory recovery. By promoting alveolar stability and gas exchange, surfactant accelerates the resolution of respiratory distress, allowing for earlier

extubation and a shorter duration of invasive respiratory support. This not only minimizes the potential complications associated with prolonged mechanical ventilation, such as ventilator-induced lung injury and infection but also facilitates a smoother transition to non-invasive respiratory support or spontaneous breathing. The observed decrease in oxygen requirement further underscores the beneficial effects of surfactants on gas exchange. By maintaining alveolar patency and optimizing the surface area available for gas diffusion, surfactant enhances oxygen uptake and carbon dioxide elimination. This translates to improved oxygenation and reduced reliance on supplemental oxygen, promoting respiratory stability and minimizing the risk of oxygen toxicity.[23-25]

While the meta-analysis did not reveal a statistically significant effect of surfactant therapy on bronchopulmonary dysplasia (BPD) incidence, the trend toward reduction warrants further consideration. BPD, a chronic lung disease affecting preterm infants, is a complex and multifactorial entity with diverse contributing factors beyond surfactant deficiency. Prematurity itself, with its associated lung immaturity and vulnerability to injury, plays a crucial role in BPD pathogenesis. Additionally, inflammation, oxidative stress, and barotrauma from mechanical ventilation can further contribute to lung damage and impair alveolar development. Surfactants, while primarily addressing surfactant deficiency, may also exert indirect protective effects on the developing lungs. By improving lung compliance and reducing the need for mechanical ventilation, surfactant may mitigate the risk of ventilator-induced lung injury and barotrauma. Furthermore, some studies suggest that surfactant may possess anti-inflammatory properties, potentially modulating the inflammatory response associated with BPD. However, the complex interplay of various factors in BPD pathogenesis likely explains the lack of a definitive effect of surfactant therapy on its incidence in the meta-analysis. Future research should focus on identifying specific subgroups of preterm infants who may be most likely to benefit from surfactant therapy in terms of BPD prevention. Additionally, exploring the optimal timing, dosing, and combination of surfactant with other lung-protective strategies may be crucial in maximizing its potential to reduce BPD risk.[26-28]

The trend towards reduced mortality with surfactant therapy, although not statistically significant, offers a glimmer of hope in improving survival rates among preterm infants. Mortality in this population is often linked to severe respiratory failure and its associated complications, such as pulmonary hemorrhage and sepsis. Surfactant's ability to enhance respiratory function and mitigate the severity of RDS may contribute to improved survival by reducing the incidence and severity of these life-threatening complications. However, the lack of statistical significance underscores the need for further research to confirm this association and identify specific subgroups of infants who may derive the greatest survival benefit from surfactant therapy. Factors such as gestational age, severity of illness, and comorbidities may influence the impact of surfactants on mortality. Future studies with larger sample sizes and longer follow-up periods are warranted to definitively establish the role of surfactants in reducing mortality among preterm infants.[27-29]

The meta-analysis revealed a trend towards reduced PDA incidence with surfactant therapy, although this did not reach statistical significance. This observation aligns with a growing body of evidence suggesting a potential beneficial effect of surfactants on cardiovascular stability in preterm infants. The pathophysiology of PDA in preterm infants is complex and multifactorial, involving interactions between the pulmonary and systemic circulations. Surfactant, by virtue of its effects on lung mechanics and pulmonary vascular tone, may play a role in modulating these interactions and influencing PDA closure. Surfactant deficiency in preterm infants leads to decreased lung compliance and increased PVR, creating a pressure gradient that favors blood flow from the aorta (high pressure) to the pulmonary artery (low pressure) through the PDA. Surfactant replacement therapy improves lung compliance and reduces PVR, thereby decreasing the pressure gradient and potentially promoting PDA closure. This mechanism is supported by studies demonstrating a

correlation between surfactant administration and decreased left-to-right shunting through the PDA.[28-30]

Inflammation plays a role in maintaining PDA patency in preterm infants. Surfactant, in addition to its primary function in reducing surface tension, possesses anti-inflammatory properties. These anti-inflammatory effects may contribute to reducing ductal inflammation and promoting its closure. Studies have shown that surfactant administration can decrease levels of inflammatory mediators associated with PDA, such as prostaglandins and cytokines. Surfactant therapy may also indirectly influence PDA closure by improving overall respiratory function and oxygenation. Hypoxemia and hypercapnia can stimulate the production of vasodilatory prostaglandins, which maintain PDA patency. By improving gas exchange and reducing respiratory distress, surfactant may indirectly contribute to PDA closure by decreasing the stimulus for prostaglandin production. While the current meta-analysis did not find a statistically significant reduction in PDA incidence, the observed trend and the supporting evidence from previous studies warrant further investigation. Future research should focus on elucidating the precise mechanisms by which surfactant influences PDA closure and identifying optimal surfactant regimens to minimize PDA risk in preterm infants.[29-31]

The significant improvements in blood pressure parameters observed in the meta-analysis highlight the potential for surfactant therapy to exert broader hemodynamic benefits beyond its primary effects on the lungs. Preterm infants are prone to hemodynamic instability due to immature cardiovascular regulatory mechanisms and the frequent presence of comorbidities such as sepsis and hypotension. Surfactant therapy, by improving lung function and oxygenation, can positively impact systemic hemodynamics. Improved lung compliance and oxygenation can lead to decreased pulmonary blood flow and increased pulmonary venous return to the left atrium. This, in turn, can increase left ventricular preload and stroke volume, leading to increased cardiac output and SVR. Increased SVR contributes to improved blood pressure and better perfusion of vital organs. Surfactant therapy's positive impact on lung function can also improve right ventricular function by reducing pulmonary vascular resistance and right ventricular afterload. This can lead to increased right ventricular output and, consequently, improved overall cardiac output. Enhanced cardiac output ensures adequate blood flow and oxygen delivery to various organs, including the brain, kidneys, and gut. The observed improvements in blood pressure parameters following surfactant administration suggest that it may play a role in stabilizing hemodynamics in preterm infants. This hemodynamic stabilization can have far-reaching implications for organ perfusion and overall cardiovascular health, potentially reducing the risk of complications associated with hypotension and hypoperfusion.[30-32]

The positive impact of surfactant therapy on cerebral blood flow velocity is a particularly significant finding. The developing brain of a preterm infant is highly vulnerable to fluctuations in cerebral blood flow and oxygen delivery. Inadequate cerebral perfusion can lead to hypoxic-ischemic injury, impaired brain development, and long-term neurodevelopmental sequelae. Surfactant therapy, by improving oxygenation and systemic hemodynamics, may enhance cerebral blood flow and oxygen delivery to the brain. The observed increase in cerebral blood flow velocity suggests that surfactant may promote optimal brain perfusion, potentially mitigating the risk of neurological complications in preterm infants. This finding underscores the importance of surfactant therapy not only for respiratory support but also for protecting the developing brain. The evidence presented in this meta-analysis highlights the multifaceted benefits of surfactant therapy in preterm neonates. Beyond its well-established role in improving respiratory outcomes, surfactant may also contribute to cardiovascular stability and enhanced cerebral perfusion. The trend towards reduced PDA incidence, improvements in blood pressure parameters, and increased cerebral blood flow velocity suggest a broader impact of surfactant on hemodynamic and neurological well-being.[31-33]

The consistent benefits of surfactant therapy across different subgroups based on gestational age,

surfactant type, and mode of administration highlight its broad applicability and effectiveness in diverse clinical scenarios. The lack of significant heterogeneity in treatment effects across these subgroups suggests that surfactant therapy can be tailored to individual patient needs without compromising its efficacy. The robustness of the findings, demonstrated by the sensitivity analyses, further strengthens the confidence in the conclusions of this meta-analysis. The consistent results even after excluding studies with high risk of bias or small sample sizes, or using a fixed-effects model, suggest that the observed benefits of surfactant therapy are not unduly influenced by methodological limitations or specific study characteristics.[32,33]

This meta-analysis has several strengths, including its comprehensive search strategy, rigorous study selection process, and use of robust statistical methods. The inclusion of both RCTs and observational studies enhances the generalizability of the findings to real-world clinical practice. The subgroup and sensitivity analyses provide additional insights into the consistency and robustness of the observed effects. However, some limitations should be acknowledged. The heterogeneity in study designs, surfactant types, and modes of administration across studies may have contributed to some degree of variability in the results. Although the random-effects model was used to account for this heterogeneity, residual confounding cannot be entirely ruled out. Additionally, the lack of long-term follow-up data in some studies limits the ability to assess the long-term impact of surfactant therapy on neurodevelopmental outcomes and other potential late complications.[32-34]

The findings of this meta-analysis have important implications for the clinical management of preterm neonates. The evidence strongly supports the use of surfactant therapy as a cornerstone in the treatment of RDS, with clear benefits in reducing the need for and duration of mechanical ventilation, improving oxygenation, and potentially enhancing hemodynamic stability and cerebral perfusion. The choice of surfactant type and mode of administration may be guided by individual patient characteristics and clinical context, as the benefits of surfactant therapy appear to be consistent across different subgroups. However, further research is needed to establish the optimal surfactant regimens for specific populations and to explore the potential long-term benefits and risks associated with surfactant therapy. This meta-analysis highlights several areas for future research. Further investigation is needed to definitively establish the impact of surfactant therapy on PDA incidence and its associated hemodynamic consequences. Long-term follow-up studies are essential to evaluate the potential long-term benefits and risks of surfactant therapy, particularly in terms of neurodevelopmental outcomes and chronic lung disease. Additionally, research exploring the optimal timing, dosing, and combination of surfactant therapy with other lung-protective strategies may lead to further improvements in outcomes for preterm infants.[33-35]

4. Conclusion

This meta-analysis provides compelling evidence supporting the beneficial effects of surfactant therapy on respiratory and hemodynamic outcomes in preterm neonates. Surfactant administration is associated with significant improvements in respiratory function, including reduced need for and duration of mechanical ventilation, and decreased oxygen requirement. Additionally, surfactant therapy may have a positive impact on hemodynamic stability, cerebral perfusion, and potentially PDA incidence. These findings underscore the critical role of surfactant therapy in improving the overall health and well-being of preterm infants.

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