Research Article

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Budesonide-Surfactant Therapy for Neonatal Respiratory Distress Syndrome in Preterm Infants: A Systematic Review and Meta-Analysis of Respiratory Outcomes

Mahmood Noorishadkam[1], Sedigheh Ekraminasab[*1,2], Seyedeh Elham Shams[3], Hossein Neamatzadeh[1]

[1] Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Department of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Department of Pediatrics, Hamadan University of Medical Sciences, Hamadan, Iran

Received: 23 October 2024 **Revised:** 20 November 2024 **Accepted:** 4 December 2024

ARTICLE INFO

Corresponding author:
Sedigheh Ekraminasab

Email:
s.ekraminasab@gmail.com

Keywords:
Pulmonary surfactant,
Neonatal respiratory distress syndrome,
Budesonide,
Meta-analysis

ABSTRACT

Background: Neonatal respiratory distress syndrome (NRDS) in preterm infants is a critical condition often necessitating urgent medical intervention. This meta-analysis assesses the efficacy and safety of combining surfactant with budesonide for treating NRDS in preterm neonates, emphasizing respiratory outcomes.

Methods: We performed a systematic review of databases (PubMed, Embase, Cochrane Library) following PRISMA guidelines from inception to July 30, 2024. Studies comparing budesonide-surfactant combination therapy to surfactant alone in NRDS were included. Respiratory outcomes evaluated included duration of mechanical ventilation, continuous positive airway pressure (CPAP), length of hospitalization, and frequency of a second surfactant dose. The outcomes were the incidence of bronchopulmonary dysplasia (BPD) and mortality rates. Data from eligible studies were pooled for meta-analysis using a random-effects model.

Results: Ten articles involving 920 infants in the treatment group and 1167 in the control group were analyzed. The combination therapy significantly reduced mechanical ventilation time, hospitalization duration, and CPAP use and decreased the need for a second surfactant dose. The treatment group also showed significantly lower mortality rates (OR = 0.694, 95% CI: 0.52, 0.927, $P < 0.05$) and BPD incidence (OR = 0.639, 95% CI: 0.525, 0.778, $P < 0.001$) compared to controls.

Conclusion: Budesonide-surfactant therapy for NRDS in preterm infants effectively reduces mechanical ventilation time and hospitalization. It also significantly lowers mortality rates, the need for a second surfactant dose, and BPD incidence, indicating its potential for widespread application in NICUs. Further large-scale trials are needed to validate these findings and assess long-term outcomes.

Introduction

Neonatal respiratory distress syndrome (NRDS) is a prevalent complication in preterm neonates, primarily caused by inadequate surfactant production, which results in respiratory difficulties and considerable morbidity.[1] While traditional treatment has relied on exogenous surfactant administration, recent research has begun to investigate adjunct therapies that could further improve outcomes.[2] NRDS poses a significant challenge in the management of premature newborns, potentially leading to complications such as bronchopulmonary dysplasia (BPD).[3,4] Current treatment strategies for NRDS include surfactant replacement therapy, continuous positive airway pressure (CPAP), and mechanical ventilation.[5] Nevertheless, the search for more effective and less invasive treatment options continues to progress in neonatal medicine.[6]

Surfactant replacement therapy remains the standard approach for NRDS; however, concerns regarding inflammation and lung injury associated with this treatment have spurred research into alternative medicines. One promising strategy involves the combination of budesonide, a corticosteroid, with surfactant administration.[7] Budesonide serves as an anti-inflammatory agent, targeting the inflammatory processes involved in the pathogenesis of NRDS. By mitigating lung inflammation, budesonide aims to reduce pulmonary injury and enhance respiratory function in preterm neonates.[8]

Several studies have indicated that the budesonide-surfactant combination may be more effective than surfactant alone. For instance, Marzban et al. found no significant difference in mortality rates or BPD between the two treatment groups; however, administering surfactant with budesonide to infants under 30 weeks gestational age significantly decreased mortality compared to surfactant alone. These results suggest that this combination therapy could be particularly advantageous for preterm infants born at less than 34 weeks gestation and weighing less than 1500 grams.[9] Conversely, Moschino et al. reported that in very preterm infants with very low birth weight (VLBW) and severe NRDS, the combination of budesonide with surfactant did not significantly impact the incidence of BPD, death, or the combined outcome of BPD or death at 36 weeks postmenstrual age. However, the combination therapy was deemed safe.[10]

Recent investigations have focused on the efficacy of combining budesonide with surfactant to enhance outcomes for preterm infants with NRDS. This meta-analysis aims to evaluate the effectiveness of budesonide-surfactant therapy in comparison with standard surfactant therapy alone, concentrating on respiratory outcomes, particularly the need for mechanical ventilation. Additionally, it will assess key outcomes such as mortality rates and the incidence of BPD. By analyzing these factors, the research provides valuable insights for neonatologists and pediatricians in shaping their treatment strategies for infants affected by NRDS.

Materials and Methods

Search Strategy

We conducted a systematic review of recent studies on the combination of budesonide and surfactant for treating neonates with NRDS, identifying relevant trials up to August 2024. Our search utilized both subject headings and text keywords related to budesonide, surfactant, RDS, BPD, mortality, and neonates across databases such as Google Scholar, Wanfang, Weipu, CNKI, PubMed, Embase, and Cochrane Library.

Study Selection

Two independent reviewers screened all citations for inclusion and extracted potentially relevant studies for full-text review. They also evaluated the full texts, resolving disagreements through consensus with a third reviewer. Inclusion criteria focused on original randomized clinical studies, cohort studies, and case-control studies comparing the budesonide-surfactant combination with surfactant alone in

NRDS neonates. We excluded systematic reviews, narrative reviews, letters, comments, preprints, abstracts, case reports, and articles not in English if data could not be extracted from the abstract.

Data Extraction and Quality Assessment

Data was abstracted and stored in a customized Excel sheet, covering study design, patient characteristics, interventions, and outcomes, including the duration and frequency of invasive ventilation, additional surfactant doses, hospitalization length, BPD incidence, and mortality rates. Variations in definitions of outcomes were noted.

Bias assessment utilized the Cochrane Collaboration risk of bias tool, evaluating random sequence generation, allocation concealment, caregiver blinding, outcome assessment, incomplete data, selective reporting, and important cointerventions. A study was deemed at high risk of bias in any domain, except for caregiver blinding, where standardization of mechanical ventilation, sedation, and weaning was accepted to reduce performance bias in these necessary unblinded trials.

Outcomes

Key outcomes included respiratory parameters such as days on mechanical ventilation, hospitalization, CPAP duration, and the number of second surfactant doses. The key outcomes in this meta-analysis were mortality rates and BPD incidence.

Statistical Analysis

We weighted studies using the inverse variance method and pooled data with a random effects model, considering a P value of 0.05 or less statistically significant. A priori subgroup analyses compared surfactant-budesonide studies to those using surfactant alone. To assess publication bias, we visually examined funnel plots of treatment effect against study precision. All statistical analyses were conducted using comprehensive meta-analysis software.

Results

Selected studies characteristics

The meta-analysis of budesonide-surfactant treatment for NRDS revealed significant findings across various outcomes. This study incorporated randomized clinical trials.[10-16] and observational studies,[17-19] concentrating on very low birth weight (VLBW) and premature newborns. A total of ten studies were analyzed, with 920 infants in the budesonide-surfactant treatment group (test group) and 1,167 infants in the surfactant-only group (control group). The gestational ages of the infants ranged from 24 to 32 weeks, and both groups received standard care for NRDS, with the addition of budesonide in the test group. Study characteristics are summarized in Table 1.

Respiratory Outcomes

Mechanical Ventilation Duration: The effect of surfactant combined with budesonide on mechanical ventilation time in infants with NRDS was assessed in five studies involving 662 children (330 in the test group and 332 in the control group). The control group required an average of 44.54 days of mechanical ventilation, compared to 28.12 days in the test group, indicating a reduction of 16 days in the test group (Table 2). Meta-analysis demonstrated that the combination of pulmonary surfactant and budesonide significantly reduced ventilation duration, with a Standardized Mean Difference (SMD) of 0.425 (95% CI: 0.270 to 0.580) and a p-value < 0.001 (Table 3, Figure 1). This suggests that budesonide may enhance respiratory stabilization, thereby decreasing risks associated with prolonged mechanical ventilation, such as ventilator-associated lung injury and infections.

CPAP Duration: In the control group, the average CPAP duration was 23.61 days, while the intervention group averaged 18.51 days, indicating a significant reduction in CPAP use with the addition of budesonide to surfactant therapy (Table 2). The pooled effect size showed an SMD of 0.280 (95% CI: 0.107 to 0.453) with a p-value < 0.001, further supporting the efficacy of this combination in reducing prolonged CPAP therapy (Table 3, Figure 2).

Table 1. Key Features of Randomized Controlled Trials and Observational Studies in the Meta-Analysis.

Author/Year	Country	Sample size	Gestational Age (weeks)	Birth Weight (g)	Intervention/Treatment
Ye et al., 2016	Taiwan/USA	131/134	26.5/26.8	<1500/<1500	Budesonide 0.25 mg/kg + Beractant 100 mg/kg
Gharehbaghi et al., 2021	Iran	64/64	<30/<30	<1500/<1500	Poractant alfa 200 mg/kg + Budesonide 0.25 mg/kg
Heo et al., 2020	South Korea	16/18	28 ± 1/28 ± 2	<1500/<1500	Calfactant 105 mg/kg + Budesonide 0.25 mg/kg
Moschino et al., 2021	Italy	18/18	<28/<28	<1500/<1500	Curosurf 200 mg/kg + Budesonide 0.25 mg/kg
Kothe et al., 2020 (	USA	173/294	26.7 ± 2.1/26.7 ± 2.1	<1250/<1250	Budesonide 0.25 mg/kg + Beractant 100 mg/kg
Baghal Safa et al., 2023	Iran	35/35	29.34 ± 2.19/29.94 ± 2.11	1139.86 ± 230.28/1186 ± 224.14	2.5cc/kg of Curosurf solution + 250 µ/kg of Palmicort
Marzban et al., 2024	Iran	67/67	31.66 ± 2.84/31 ± 2.96	1584.55 ± 505.02/1465.45 ± 520.88	NA
Armanian et al., 2023	Iran	95/95	28.94 ± 1.57/29.015 ± 1.57	1134.97 ± 237.61/1190 ± 289.33	Each infant received Budesonide once at a dose of 0.25 mg/kg (0.5 cc/kg)
Anderson et al., 2021	USA	173/294	26.7 ± 2.1/26.7 ± 2.1	≤1250/≤1250	Budesonide 0.25 mg/kg mixed with Beractant surfactant 4 mL/kg
Kashaki et al., 2023	Iran	148/148	<37/<37	<1500/<1500	Surfactant (Braksurf) + Budesonide 0.25 mg/kg

In this table, the left numbers represent the test group (surfactant and Budesonide) and the right numbers represent the control group (solely of surfactant.)

Table 2. Comparison of outcomes of respiratory support in neonates with NRDS between two groups

Study	Number		Hospitalization (day)		Second Dose of Surfactant (n)		MV (day)		CPAP (day)	
	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control
Gharehbaghi et al., 2021	64	64	-	-	-	-	1.38	5.50	4.04	5.21
Heo et al., 2020	16	18	73.2	91.9	5	8	14.7	26.3	-	-
Moschino et al., 2021	18	18	-	-	-	-	-	-	5	3
Kothe et al., 2020	166	280	-	-	-	-	-	-	-	-
BaghalSafa et al., 2023	35	35	30.11	42.23			3.60	6.11	7.77	13.90
Marzban et al., 2024	67	67	16.15	16.21	13	41	2.85	4.37	-	-
Kashaki et al., 2023	148	148	4.75	27.51	25	47	5.59	2.26	1.7	1.5
Total	514	630	124.21	177.85	43	96	28.12	44.54	18.51	23.61

Test: surfactant+ Budesonide; Control: surfactant; MV: mechanical ventilation

Table 3. Summary estimates for respiratory outcomes in NRDS patients

Subgroup	Type of Model	Heterogeneity		Effect size and 95% CI					Publication Bias	
Overall	Fixed	I^2 (%)	P_H	Variance	SMD	95% CI	Z_{test}	P_{OR}	P_{Begg}	P_{Egger}
MV	Fixed	56.886	0.055	0.006	0.425	0.270-0.580	5.38	0.000	0.462	0.306
CPAP	Fixed	86.718	0.000	0.008	0.280	0.107-0.453	3.176	0.001	0.308	0.244
Hospitalization	Fixed	74.680	0.008	0.008	0.478	0.305-0.651	5.412	0.000	1.00	0.664

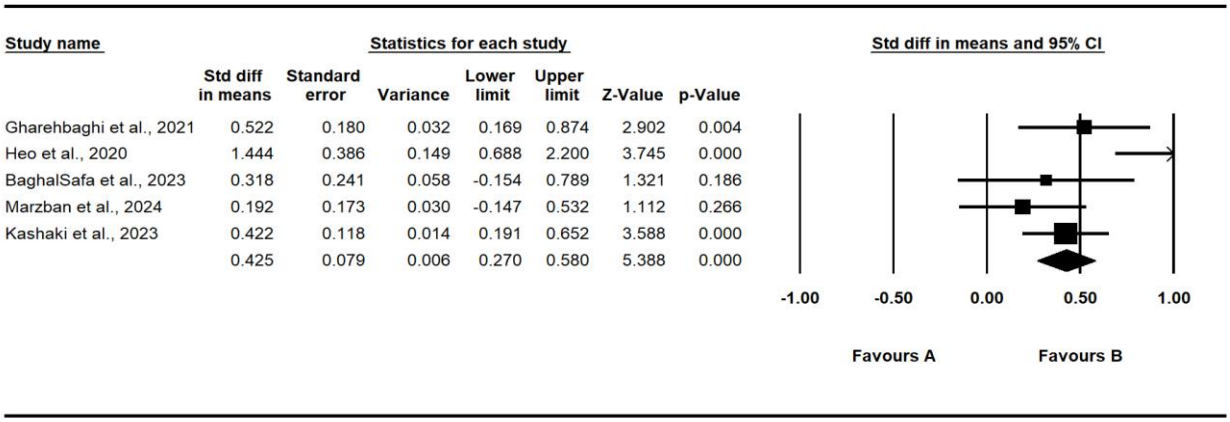

Figure 1. meta-analysis of the duration of Mechanical Ventilation between two groups
Favours A: test group; Favours B: control group

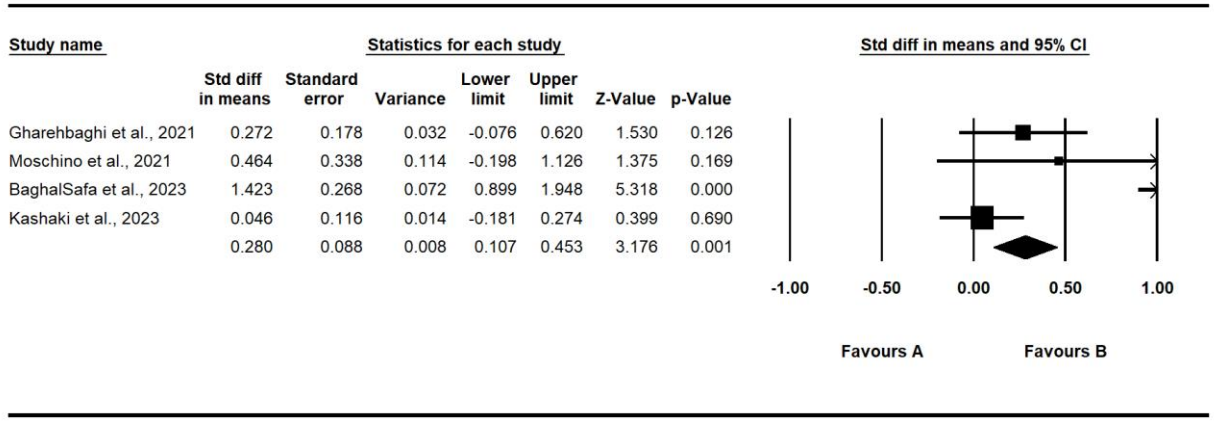

Figure 2. meta-analysis of the duration of CPAP between two groups

Length of Hospital Stay: Four studies reported on the length of hospital stay, including 534 newborns (266 in the test group and 268 in the control group) (Table 2). The meta-analysis indicated that the budesonide-surfactant combination significantly shortened hospitalization duration, with an overall SMD of 0.478 (95% CI: 0.305 to 0.651) and a p-value < 0.001 (Table 3, Figure 3). Infants in the test group experienced an average reduction of 53 days in hospital stay (Table 2), suggesting improved respiratory outcomes and fewer RDS-related complications.

Second Dose of Surfactant: The need for a second dose of surfactant was significantly lower in the test group, with only 8.4% of infants requiring it compared to 15.2% in the control group (odds ratio (OR) = 0.326; 95% CI: 0.212, 0.50; P < 0.001) (Table 2). This reduction indicates enhanced initial efficacy in

respiratory stabilization with the budesonide-surfactant combination, potentially lowering the risks and costs of repeated dosing (Figure 4).

Mortality Rate: Ten studies reported a total of 230 deaths, with 85 in the test group and 145 in the control group. The mortality rate was 16.5% in the test group compared to 23% in the control group, demonstrating a significantly lower mortality risk with the budesonide-surfactant combination (OR = 0.694; 95% CI: 0.52, 0.927; P < 0.05) (Table 4, Figure 5). This indicates a potential life-saving benefit, especially for infants with extremely low birth weight. The statistical analysis showed P=0.882, and I2=0.00%, justifying the use of a fixed-effect model (Table 5).

BPD Incidence: All ten studies reported BPD incidence among 2,087 neonates (920 in the experimental group and 1,167 in the control group). The analysis indicated an OR of 0.639 (95% CI: 0.525–0.778; P<0.0001) (Figure 6), suggesting that the budesonide-surfactant combination significantly reduces BPD incidence, which is crucial as BPD contributes to chronic respiratory issues and neurodevelopmental challenges in preterm infants. The anti-inflammatory properties of budesonide likely play a key role in mitigating lung injury that leads to BPD.

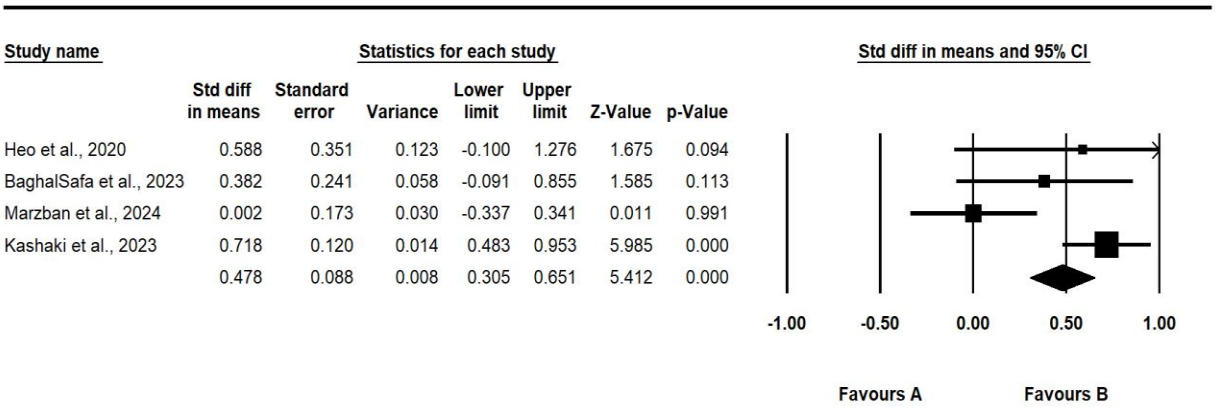

Figure 3. meta-analysis of the duration of hospitalization between two groups

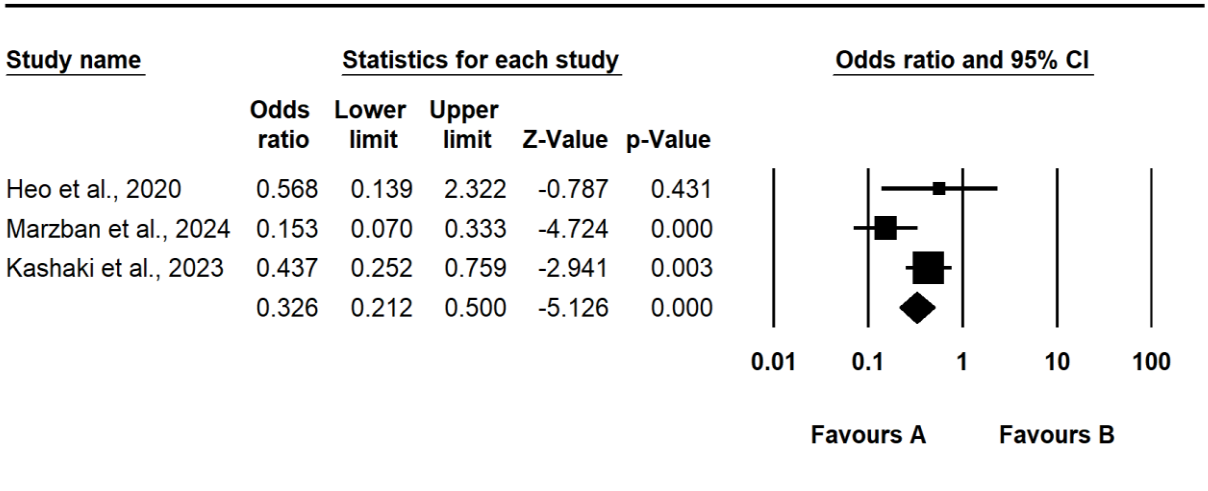

Figure 4. meta-analysis of the incidence of second dose between two groups

Table 4. Comparison of outcomes in neonates with NRDS between two groups

Study	Sample Size	Mortality		BPD	
		Test	Control	Test	Control
Yeh et al., 2016	265	17	22	38	67
Gharehbaghi et al., 2021	128	6	9	24	38
Heo et al., 2020	34	1	4	5	8
Moschino et al., 2021	36	1	0	8	9
Kothe et al., 2020	467	15	31	74	155
BaghalSafa et al., 2023	70	4	9	3	14
Marzban et al., 2024	134	10	19	8	10
Armanian et al., 2023	190	13	15	46	48
Anderson et al., 2021	467	15	31	106	187
Kashaki et al., 2023	296	3	5	4	13
Total	2087	85	145	316	549

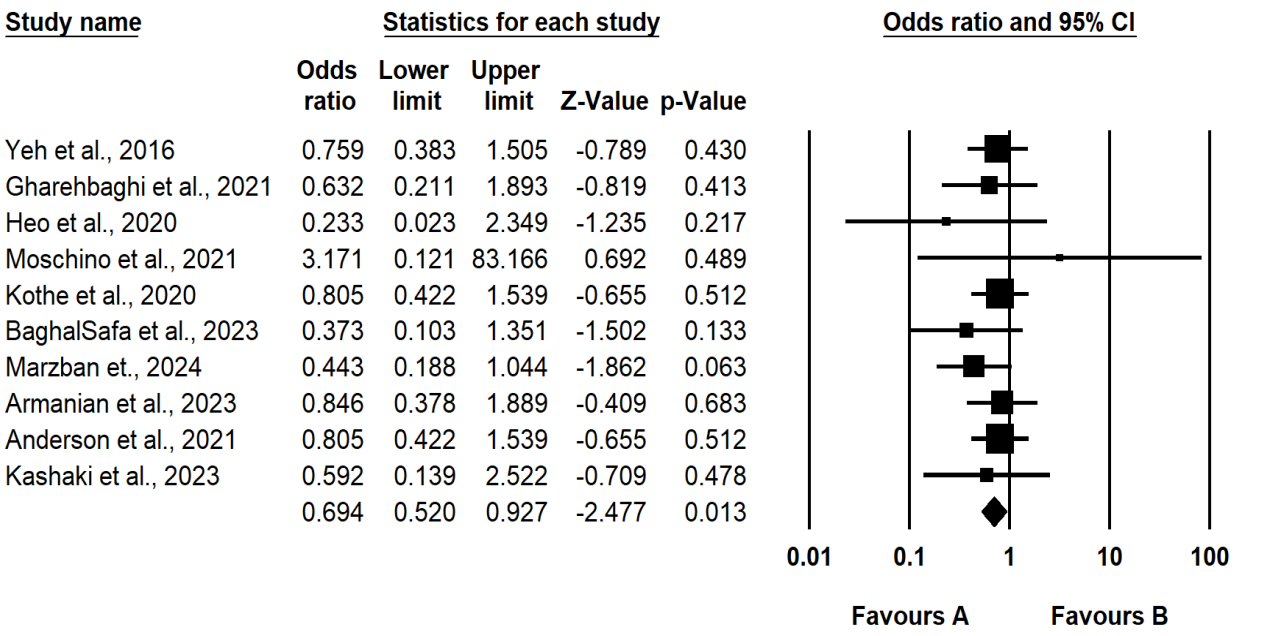

Figure 5. meta-analysis of the incidence of mortality between two groups

Table 5. Summary estimates for outcomes and second dose of surfactant in NRDS patients

Subgroup	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
Overall	Fixed	I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Begg}	P_{gger}
Mortality	Fixed	0.000	0.882	0.694	0.52-0.927	-2.477	0.013	-2.51	0.012
BPD	Fixed	44.050	0.065	0.639	0.525-0.778	-4.474	0.000	-4.85	0.000
Second Dose of Surfactant	Fixed	62.357	0.070	0.326	0.212-0.500	-5.126	0.000	1.000	0.959

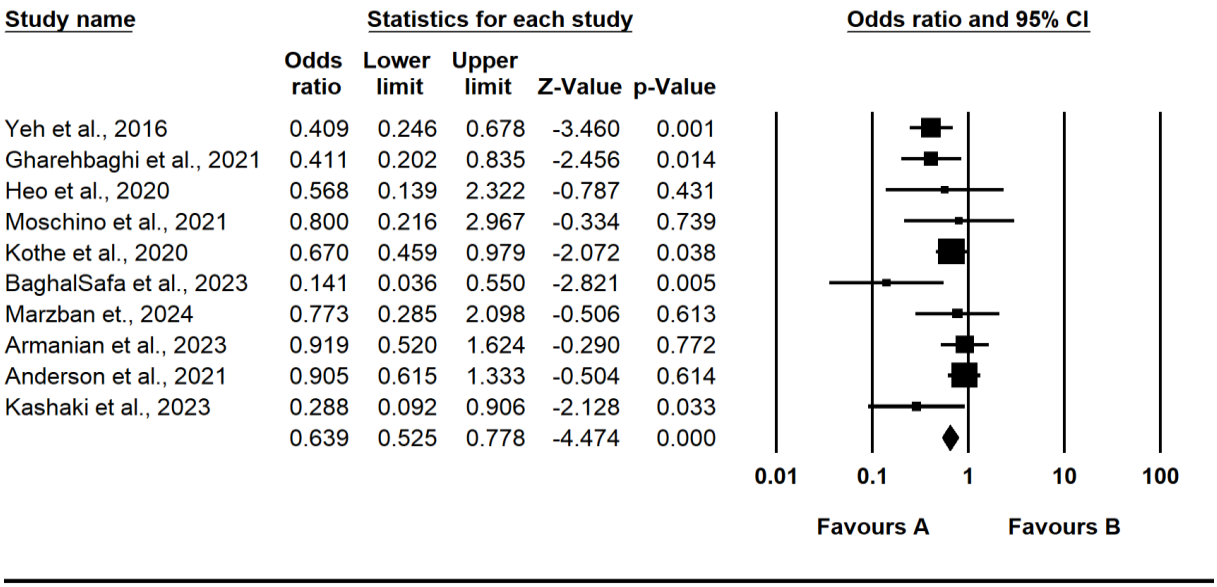

Figure 6. meta-analysis of the incidence of BPD between two groups

Discussion

In this study, we evaluated the effectiveness of a budesonide-surfactant combination compared to surfactant alone in treating NRDS, to reduce complications. Our meta-analysis indicates that the duration of respiratory support was shorter in the budesonide-surfactant group than in the surfactant-only group. Furthermore, the administration of the budesonide-surfactant mixture was associated with a reduced risk of BPD and mortality in preterm infants. All included studies reported decreases in BPD and mortality rates using the budesonide-surfactant combination.

The most recent systematic reviews before this study were conducted by Zongyan Yi et al. in 2022. [20] Similar to our findings, they demonstrated that combining pulmonary surfactant infusion therapy with budesonide therapy effectively reduced the duration of mechanical ventilation, length of hospital stay, and incidence of BPD.[20] Several studies have shown promising outcomes, particularly in reducing BPD incidence and improving respiratory function in preterm infants. Yeh et al. (2016) reported a decrease in BPD or death in both studies, with a specific reduction in BPD observed.[11] In the study by Gharehbaghi et al., the intervention group showed a notably lower rate of BPD. Notably, subgroup analysis indicated that administering a combination of surfactant and budesonide to infants under 30 weeks of age significantly decreased mortality compared to surfactant alone. However, no statistically significant differences were observed between the groups for primary outcomes.[12] A cohort study by Kothe et al. found no significant differences in the incidence of BPD, death, or the composite outcome of BPD or death when using combination therapy. Nonetheless, budesonide was associated with a decrease in the need for prolonged mechanical ventilation, severe BPD type II or death, and grade III BPD or death.[18]

Interestingly, some studies have reported secondary benefits of the combination therapy. For instance, infants treated with budesonide-surfactant exhibited a lower rate of admissions to pediatric wards due to respiratory infections within the first year of corrected age.[10] This finding suggests potential long-term respiratory benefits that merit further investigation. The method of administration appears to affect the treatment's efficacy, with subgroup analyses showing that tracheal instillation of budesonide-surfactant was more effective

than nebulization in reducing mechanical ventilation time and length of hospital stay.[10, 20, 21] This information could be valuable for clinicians when deciding on the most appropriate administration method. The mechanism behind budesonide's effectiveness in improving respiratory function and preventing BPD is multifaceted. It acts as a local anti-inflammatory glucocorticoid, increases the synthesis of pulmonary surfactant, and possesses antioxidant properties.[22] Additionally, it inhibits the synthesis of prostaglandins and leukotrienes, which are involved in inflammation[14]. Budesonide-surfactant therapy combines the anti-inflammatory properties of budesonide with the surface-tension-reducing effects of surfactant. This synergistic approach addresses both the structural immaturity of the lungs and the inflammatory cascade associated with NRDS.[23, 24]

The safety profile of budesonide-surfactant combination therapy is a crucial aspect to evaluate. Although most studies have not shown a significant increase in adverse effects or mortality rates associated with the treatment, some safety concerns require careful attention. The absorption of budesonide into the bloodstream has been observed, with effects on blood cortisol suppression and other blood metabolites varying based on dosage.[25] A study involving dose escalation indicated that even at the lowest tested dose of 0.025 mg/kg, minimal systemic metabolic effects were noted while still effectively reducing lung inflammation in infants with elevated inflammatory status[25]. This suggests that lower doses could potentially achieve a better balance between effectiveness and safety.

The meta-analysis of budesonide-surfactant for NRDS treatment has highlighted its potential benefits and limitations. While some studies indicate promise in reducing BPD and improving respiratory function, particularly in very premature infants, other research has found no significant differences in key outcomes. This variability underscores the need for further research to fully understand the treatment's effectiveness. The safety profile of the combination therapy also requires careful consideration, with some studies reporting potential benefits while others raise concerns about infection risks. Clinicians should weigh the pros and cons carefully when considering this treatment, considering factors such as the infant's age, the severity of NRDS, and any other health issues the infant may have.

Overall, the findings support the effectiveness of budesonide-surfactant combination therapy in reducing the duration of mechanical ventilation, minimizing the need for additional interventions, and improving survival rates in NRDS. These outcomes suggest that adjunctive budesonide with surfactant could offer substantial clinical benefits, particularly for very premature infants at high risk for long-term respiratory and developmental issues. Further studies are encouraged to validate these findings and optimize treatment protocols for this vulnerable population. It is suggested that future analyses could benefit from additional subgroup analyses considering different drug dosages to enhance the accuracy and reliability of the results.

Limitations of this research

The innovation of this study lies in its focus on the clinical treatment of neonatal distress syndrome and the outcomes associated with the budesonide-surfactant combination. Given that most of the studies did not report respiratory outcomes such as duration of ventilation and CPAP, and considering the relatively small sample size of the included studies, there are limitations to the findings. Additionally, most included studies did not describe data blinding, which may introduce selection bias. Furthermore, there is no uniform standard for drug dosage and frequency of administration in the current treatment protocols.

Conclusion

This study supports the potential benefits of budesonide-surfactant combination therapy for treating NRDS by demonstrating reductions in respiratory support duration and improved outcomes, such as decreased BPD and mortality in preterm infants. These findings align with previous research, showing the combination therapy's effectiveness in reducing BPD incidence, length of hospital stay, and mechanical ventilation needs, particularly in very premature infants. While the results are promising, there is some inconsistency across studies regarding outcomes and safety, highlighting the need for further research to confirm these findings and address remaining safety concerns. The absorption of budesonide and potential systemic effects, such as cortisol suppression, emphasize the importance of evaluating dosing strategies. The method of administration also appears to impact outcomes, with tracheal instillation showing greater effectiveness than nebulization. Additionally, lower doses of budesonide may balance efficacy with a reduced risk of adverse effects. Given the mixed evidence, clinicians should consider each infant's needs, NRDS severity, and other health factors when selecting this therapy. Further large-scale, well-designed studies are essential to optimize dosing, administration methods, and treatment protocols for this vulnerable population. With continued research, the budesonide-surfactant combination could offer a valuable approach to improving respiratory outcomes and survival in infants with NRDS.

Conflict of Interest

All authors declare no conflicts of interest.

Acknowledgments

The authors thank the editors and anonymous reviewers for their insightful suggestions.

Funding

This study received no funding.

Author's Contribution

Conceptualization, M.N., S.E., H.N.; Methodology, H.N., S.E.; Formal analysis, S.E., H.N.; Investigation, S.E., H.M., S.S.; Resources, S.E., M.N.; Data curation, S.E., S.S.; Writing—original draft, S.E.; Writing—review and editing, M.N., H.N.; Supervision, M.N., S.E. All authors have read and approved the final manuscript.

How to Cite: Noorishadkam M, Ekraminasab S, Shams SE, Neamatzadeh H. Budesonide-Surfactant Therapy for Neonatal Respiratory Distress Syndrome in Preterm Infants: A Systematic Review and Meta-Analysis of Respiratory Outcomes. World J Peri & Neonatol 2024; 7(1): 16-27.
DOI: 10.18502/wjpn.v7i1.17324

References

1. Golshan-Tafti M, Bahrami R, Dastgheib SA, Lookzadeh MH, Mirjalili SR, Yeganegi M, et al. A Comprehensive Compilation of Data on the Relationship Between Surfactant Protein-B (SFTPB) Polymorphisms and Susceptibility to Neonatal Respiratory Distress Syndrome. Fetal Pediatr Pathol 2024; 43(5): 399-418.
2. Yadav S, Lee B, Kamity R. Neonatal respiratory distress syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
3. Ekhaguere OA, Okonkwo IR, Batra M, Hedstrom AB. Respiratory distress syndrome management in resource limited settings-Current evidence and opportunities in 2022. Front Pediatr 2022; 10: 961509.
4. Bahrami R, Golshan-Tafti M, Dastgheib SA, Alijanpour K, Yeganegi M, Lookzadeh MH, et al. A comprehensive consolidation of data on the relationship between Surfactant Protein-B (SFTPB) Polymorphisms and Susceptibility to Bronchopulmonary Dysplasia. Fetal Pediatr Pathol 2024; 43(6): 436-54.
5. Daya A, Lookzadeh MH, Noorishadkam M, Mirjalili SR, Ekraminasab S. The effect of the iranian surfactant (Beraksurf) in the treatment of respiratory distress syndrome in premature neonates. World J Peri Neonatol 2023; 6(1): 10-6.

6. Ng EH, Shah V. Guidelines for surfactant replacement therapy in neonates. Paediatr Child Health 2021; 26(1): 35-49.
7. El-Gendy N, Kaviratna A, Berkland C, Dhar P. Delivery and performance of surfactant replacement therapies to treat pulmonary disorders. Ther Deliv 2013; 4(8): 951-80.
8. Elfarargy MS, Al-Ashmawy GM, Abu-Risha SM, Khattab HA. Inhaled Budesonide in Neonatal Respiratory Distress Syndrome of Near-Term Neonates: A Randomized, Placebo-Controlled Trial. J Pediatr Pharmacol Ther 2022; 27(1): 38–44.
9. Marzban A, Mokhtari S, Tavakkolian P, Mansouri R, Jafari N, Maleki A. The impact of combined administration of surfactant and intratracheal budesonide compared to surfactant alone on bronchopulmonary dysplasia (BPD) and mortality rate in preterm infants with respiratory distress syndrome: a single-blind randomized clinical. BMC Pediatr 2024; 24(1): 262.
10. Moschino L, Nardo D, Bonadies L, Stocchero M, Res G, Priante E, et al. Intra-tracheal surfactant/budesonide versus surfactant alone: Comparison of two consecutive cohorts of extremely preterm infants. Pediatr Pulmonol 2021; 56(7): 2114–24.
11. Yeh TF, Chen CM, Wu SY, Husan Z, Li TC, Hsieh WS, et al. Intratracheal administration of budesonide/surfactant to prevent bronchopulmonary dysplasia. Am J Respir Crit Care Med 2016; 193(1): 86–95.
12. Gharehbaghi MM, Ganji S, Mahallei M. A randomized clinical trial of intratracheal administration of surfactant and budesonide combination in comparison to surfactant for prevention of bronchopulmonary dysplasia. Oman Med J 2021; 36(4): e289.
13. Heo M, Jeon GW. Intratracheal administration of budesonide with surfactant in very low birth weight infants to prevent bronchopulmonary dysplasia. Turk J Pediatr 2020; 62(4): 551-9.
14. Baghal Safa F, Noorishadkam M, Lookzadeh MH, Mirjalili SR, Ekraminasab S. Budesonide and Surfactant Combination for Treatment of Respiratory Distress Syndrome in Preterm Neonates and Evaluation Outcomes. J Clin Neonatol 2023; 12(4): 135–41.
15. Marzban A, Mokhtari S, Tavakkolian P, Mansouri R, Jafari N, Maleki A. The impact of combined administration of surfactant and intratracheal budesonide compared to surfactant alone on bronchopulmonary dysplasia (BPD) and mortality rate in preterm infants with respiratory distress syndrome: a single-blind randomized clinical. BMC Pediatr 2024; 24(1): 262.
16. Armanian AM, Iranpour R, Lotfi A, Amini R, Kahrizsangi NG, Jamshad A, et al. Intratracheal Administration of Budesonide-instilled Surfactant for Prevention of Bronchopulmonary Dysplasia: A Randomized Controlled Clinical Trial. Iran J Neonatol. 2023;14(4): 1-7.
17. Kashaki M, Norouzi E, Daryasari AA, Maleki M, Farhanian F. Simultaneous intratracheal administration of surfactant and budesonide in the prevention of bronchopulmonary dysplasia in the treatment of respiratory distress syndrome in premature infants. Adv Life Sci 2023; 10(2): 304–8.
18. Kothe TB, Sadiq FH, Burleyson N, Williams HL, Anderson C, Hillman NH. Surfactant and budesonide for respiratory distress syndrome: an observational study. Pediatr Res 2020; 87(5): 940–5.
19. Anderson CD, Kothe TB, Josephsen JB, Sadiq FH, Burleyson N, Williams HL, et al. Budesonide mixed with surfactant did not affect neurodevelopmental outcomes at 6 or 18 months corrected age in observational cohorts. J Perinatol 2021; 41(7): 1681-9.
20. Yi Z, Tan Y, Liu Y, Jiang L, Luo L, Wang L, et al. A systematic review and meta-analysis of pulmonary surfactant combined with budesonide in the treatment of neonatal respiratory distress syndrome. Transl Pediatr 2022; 11(4): 526-36.
21. Manley BJ, Kamlin COF, Donath S, Huang L, Birch P, Cheong JLY, et al. Intratracheal budesonide mixed with surfactant to increase survival free of bronchopulmonary dysplasia in extremely preterm infants: study protocol for the international, multicenter, randomized PLUSS trial. Trials 2023; 24(1): 320.
22. Yao Y, Zhang G, Wang F, Wang M. Efficacy of budesonide in the prevention and treatment of bronchopulmonary dysplasia in premature infants and its effect on pulmonary function. Am J Transl Res 2021; 13(5): 4949–58.
23. Moraes LHA, Coelho RMD, Neves Dos Santos Beozzo GP, Yoshida R de AM, de Albuquerque Diniz EM, de Carvalho WB. Use of budesonide associated with a pulmonary surfactant to

prevent bronchopulmonary dysplasia in premature newborns - A systematic review. J Pediatr (Rio J) 2023; 99(2): 105-11.
24. Hillman NH, Kothe TB, Schmidt AF, Kemp MW, Royse E, Fee E, et al. Surfactant plus budesonide decreases lung and systemic responses to injurious ventilation in preterm sheep. Am J Physiol Lung Cell Mol Physiol 2020; 318(1): L41-L48.
25. McEvoy CT, Ballard PL, Ward RM, Rower JE, Wadhawan R, Hudak ML, et al. Dose-escalation trial of budesonide in surfactant for prevention of bronchopulmonary dysplasia in extremely low gestational age high-risk newborns (SASSIE). Pediatr Res 2020; 88(4): 629-36.