Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Exploring the Effects of Prone Position Ventilation Combined with Drug on Clinical Outcomes in Neonates with ARDS: A Single-Center Retrospective Cohort Study

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Objective: To evaluate the association of prone position ventilation combined with intravenous ambroxol versus conventional supine ventilation on clinical outcomes in neonates with acute respiratory distress syndrome (ARDS).

Methods: Neonates with ARDS admitted to the Neonatal Intensive Care Unit (NICU) of the Second Affiliated Hospital of Fujian Medical University between January 2023 and December 2024 were included. A total of 80 neonates were allocated into two groups (n=40 each) based on a temporal shift in clinical practice: an Observation Group receiving prone positioning (target >16 hours/day) plus intravenous ambroxol (7.5 mg/kg twice daily for 5 days), and a Control Group receiving supine ventilation alone. Both groups received standard lung-protective ventilation and co-interventions per protocol. The primary outcome was ventilator-free days (VFDs) to day 28.

Results: The primary outcome, VFDs, was significantly higher in the observation group (median [IQR]: 18 [15–21] days) than in the control group (14 [10–17] days; P=0.003). The observation group also had a shorter duration of mechanical ventilation (mean difference: 2.04 days; 95% CI: 1.55 to 2.53; P<0.001) and a shorter hospital length of stay (mean difference: 6.55 days; 95% CI: 5.61 to 7.49; P<0.001). Physiological parameters improved more favorably in the observation group, with a significant Group × Time interaction for the Oxygenation Index (P<0.001) and a lower peak inspiratory pressure at 72 hours (adjusted mean difference: −1.95 cmH_2O; 95% CI: −2.45 to −1.45; P<0.001). The overall incidence of major complications was lower in the observation group (12.5% vs. 47.5%; Relative Risk: 0.26; 95% CI: 0.11 to 0.62; P=0.001).

Conclusion: In this cohort, the combination therapy was associated with significantly improved respiratory outcomes and a lower complication rate in neonates with ARDS, suggesting it may be a beneficial adjunctive strategy. These findings warrant validation in a prospective randomized trial.

Keywords: neonatal acute respiratory distress syndrome, prone position ventilation, drug therapy, combined therapy

Introduction

Neonatal respiratory distress syndrome (NRDS) continues to pose significant challenges in neonatal care, being a leading cause of morbidity and mortality in NICUs.[1] Its pathophysiology, primarily characterized by a deficiency of pulmonary surfactant and exacerbated by an inflammatory cascade, leads to progressive alveolar collapse, severe hypoxemia, and respiratory failure.[2,3] The management of NRDS is multifaceted, involving two cornerstone strategies: mechanical ventilation to maintain gas exchange and pharmacological therapy to address the underlying biochemical deficit.[4–6]

Despite these established therapies, outcomes for severe NRDS can be suboptimal, driving the search for adjunctive strategies.[7–9] Prone positioning has emerged as a potent intervention in adult and pediatric ARDS, with robust evidence demonstrating improved oxygenation and reduced mortality in severe cases.[10–12]

https://doi.org/10.2147/TCRM.S578819
Received: 3 November 2025
Accepted: 8 March 2026
Published: 30 April 2026

However, its application in neonates, particularly preterm infants, is less standardized and supported by lower levels of evidence. Unique challenges in this population include the risk of pressure sores, airway obstruction, and the need for specialized nursing care.

Furthermore, while drugs like ambroxol, with its mucolytic and potential surfactant-stimulating properties, are sometimes used off-label, their efficacy as an adjunctive therapy in a structured protocol with prone positioning is not well-established.

Based on the physiological plausibility and the clinical need for improved adjunctive therapies, we hypothesized that the combination of prone position ventilation and intravenous ambroxol would lead to a clinically significant improvement in respiratory status compared to conventional supine ventilation alone.

Materials and Methods

Study Design

This retrospective cohort study screened neonates with Acute Respiratory Distress Syndrome (ARDS) admitted between January 2023 and December 2024. The observation and control groups were treated during the same period. This study was conducted after obtaining approval from the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University (Approval Number: 2021–094). The study was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. Given the retrospective nature of the study, which involved the analysis of anonymized pre-existing clinical data, the requirement for informed consent was formally waived by the ethics committee. All patient data were handled with strict confidentiality throughout the research process.

Patient Selection and Group Allocation

Clinical medical records were screened. To ensure cohort consistency and minimize selection bias, a consecutive sampling method was employed. A total of 80 neonates who met the inclusion criteria were included. To enhance the comparability between the two non-randomized groups, we implemented a matching strategy based on key baseline characteristics, including gestational age (±1 week), birth weight (±100g), and the initial Oxygenation Index (OI) at admission (±2). Group assignment was determined by clinical practice at the time of admission; the prone position combined with Ambroxol was increasingly adopted as a unit protocol later in the study period, whereas conventional supine ventilation was the standard approach earlier. This temporal shift in practice, rather than individual patient severity, was the primary driver of group allocation. To address potential confounding by treatment indication, we confirmed through chart review that patients in the Control Group had no documented contraindications to prone positioning (eg, unstable spinal fractures, anterior mediastinal masses). Using continuous sampling method, the compliance of exclusion criteria is confirmed by reviewing the original data such as ventilator parameters, blood gas analysis results, and discharge summary in the electronic medical record system, combined with the department's quality control nurse's secondary verification mechanism. Furthermore, we verified that no patients in the Control Group received prone positioning or Ambroxol during the study period, and similarly, no patients in the Observation Group received only one of the two interventions.

Inclusion Criteria

Inclusion criteria: (1) Diagnosis of neonatal respiratory distress syndrome (NRDS) according to the criteria defined in Practical Neonatology (7th edition).[13,14] (2) Failure of initial non-invasive respiratory support, necessitating invasive mechanical ventilation. (3) Availability of complete clinical data. (4) Baseline disease severity assessment, including an initial Oxygenation Index (OI) >8, and availability of key blood gas parameters (pH, $PaCO_2$) and chest X-ray findings at admission.

Exclusion criteria: (1) Congenital metabolic abnormalities or genetic syndromes. (2) Conditions requiring surgical intervention. (3) Major congenital heart disease or severe hemodynamic instability requiring high-dose inotropic support at admission. (4) Incomplete medical records, particularly missing key ventilator parameters, blood gas analyses, or outcome data.

Methods

Standard Care (Both Groups): All neonates received comprehensive standard care, including management of primary conditions, airway maintenance, circulatory support, infection control, and nutritional therapy. Sedation and analgesia were administered per unit protocol, primarily using continuous infusions of midazolam and/or fentanyl, to ensure patient comfort and ventilator synchrony during positioning and mechanical ventilation. Lung-protective ventilation with low tidal volume (4–6 mL/kg) was implemented using assist/control ventilation with volume guarantee (A/C+VG) mode. Initial ventilator settings were: PEEP 6–8 cmH_2O, PIP 20–25 cmH_2O, RR 30–40 breaths/min, Ti 0.4–0.5 s, and FiO_2 50%-60%. Parameters were titrated to maintain SpO_2 between 90%-95%. Co-interventions were standardized and recorded: Surfactant Therapy: Administered as rescue therapy for neonates with an OI >15. The dose and timing (first dose within 2 hours of intubation if criteria met) were recorded. Vasodilators (eg, Milrinone, iNO): Initiated upon echocardiographic confirmation of Persistent Pulmonary Hypertension of the Newborn (PPHN) with a pre-post ductal SpO_2 difference >5%, and inadequate response to optimized ventilation. ECMO Referral: Considered for refractory hypoxemia with OI >35.

Control Group: Received conventional mechanical ventilation in the supine position.

Observation Group: Received prone position ventilation combined with Ambroxol therapy.

Prone Positioning: Performed manually by 2–3 trained staff. Prior to positioning, the security of the endotracheal tube, vascular access lines, and other catheters was verified. A standardized, pressure-relieving mattress and gel pads were used to protect vulnerable areas (face, knees, thorax). A cyclical schedule was used: 4 hours in the prone position followed by 1 hour in a lateral position, aiming for a cumulative daily prone duration of >16 hours. Positioning was only performed in hemodynamically stable neonates (mean arterial pressure within the normal range for gestational age without escalating inotropic support). The procedure was immediately terminated for acute desaturation (SpO_2 drop >10% for >2 minutes), hemodynamic instability (eg, sudden bradycardia), or accidental extubation/dislodgement of critical lines. Adherence to the prone schedule and any reasons for early termination were documented in the nursing records.

Pharmacological Therapy: Ambroxol hydrochloride (Hainan Weikang Pharmaceutical Co., Ltd., National Medicine Standard H20090230) was administered intravenously at a dose of 7.5 mg/kg twice daily, dissolved in 5% glucose injection to a final volume of 5 mL, infused over no less than 5 minutes. The treatment commenced on the first day of prone positioning and continued for 5 consecutive days. Vital signs, including heart rate and oxygen saturation, were closely monitored during and for 30 minutes after the infusion to identify potential adverse drug reactions such as bradycardia, hypotension, or allergic manifestations (eg, rash). For very low birth weight (VLBW) infants (<1500g), the infusion rate was carefully controlled, and vital signs were closely monitored for potential adverse effects.

Research Indices

The primary outcome was the composite treatment success, defined as liberation from mechanical ventilation within 14 days of treatment initiation without meeting criteria for ECMO or mortality. Secondary outcomes included:

Oxygenation and Ventilation Parameters

Arterial blood gas samples were drawn at standardized time points: T0 (baseline, pre-intervention), T1 (24 hours post-intervention), and T2 (72 hours post-intervention). Parameters recorded included pH, $PaCO_2$, and OI (OI = [FiO_2 × Mean Airway Pressure] / PaO_2).

Ventilator Parameters and Support Duration

Peak Inspiratory Pressure (PIP), Positive End-Expiratory Pressure (PEEP), and FiO_2 were recorded daily. The duration of mechanical ventilation (hours) and total oxygen therapy (hours) were calculated.

Clinical Progress Indicators

Time to significant airway clearance (defined as the time from ventilation weaning to the point where suctioning was required less than once every 4 hours) and total hospital length of stay (days).

Hemodynamic Monitoring

Heart Rate (HR) and Mean Arterial Pressure (MAP) were monitored non-invasively using PHIHPS monitoring equipment at T0 and T1.

Complication Rates

The incidence of predefined complications during the hospitalization, including pneumothorax, intracranial hemorrhage (≥Grade II), and ventilator-associated pneumonia (using standardized clinical criteria), was documented. Additionally, intervention-specific safety outcomes were systematically recorded: for prone positioning, these included the incidence of pressure injuries (graded by stage), unplanned extubation, and displacement of central venous lines; for Ambroxol, documented adverse events included bradycardia, gastrointestinal intolerance (eg, vomiting), and hypersensitivity reactions.

Statistical Analysis

The sample size was estimated based on a preliminary review of our institutional data, anticipating a 25% absolute improvement in the primary outcome (composite success) in the observation group. With an alpha of 0.05 and power of 80%, a minimum of 38 patients per group was required. Statistical analyses were performed using SPSS 26.0. Continuous data were tested for normality using the Shapiro–Wilk test. Normally distributed data were presented as mean ± standard deviation and compared using the independent samples *t*-test for inter-group comparisons and repeated-measures ANOVA for within-group changes over time (T0, T1, T2). Non-normally distributed data were presented as median (interquartile range) and compared using the Mann–Whitney *U*-test. Categorical data were expressed as counts (percentages) and compared using the Chi-square test or Fisher's exact test, as appropriate. To adjust for potential baseline confounders (eg, gestational age, birth weight, initial OI, surfactant use), a multivariable logistic regression analysis was planned for the primary outcome. A two-tailed $p < 0.05$ was considered statistically significant. No adjustment for multiple comparisons was made for secondary outcomes, which were considered exploratory.

Results

Patient Flow and Baseline Characteristics

A total of 80 neonates who met the inclusion criteria were included in the final analysis, with 40 in each group. A Consolidated Standards of Reporting Trials (CONSORT)-style flow diagram for the cohort is provided in Figure 1, detailing patient screening, exclusion reasons, and final allocation. The baseline demographic and clinical characteristics of the two groups are summarized in Table 1. There were no statistically significant differences between the groups in terms of gender distribution, gestational age, or birth weight (all $P > 0.05$). The distribution of the primary diagnosis (Pneumonia, Asphyxia, or Meconium Aspiration Syndrome) was also similar between the two groups ($P = 0.814$). Critically, key indicators of initial disease severity, including the Oxygenation Index (OI), arterial pH, and $PaCO_2$ at admission, were well-balanced (all $P > 0.05$). Furthermore, the rates of key co-interventions (surfactant and vasodilator administration) and the duration of respiratory support prior to enrollment showed no significant differences, reinforcing the comparability of the two cohorts at baseline (See Appendix).

Primary and Secondary Clinical Outcomes

The primary outcome, ventilator-free days (VFDs) at day 28, was significantly higher in the observation group compared to the control group (median [IQR]: 18 [15–21] days vs. 14 [10–17] days; $P = 0.003$). Consistent with this, the duration of mechanical ventilation and total oxygen therapy were both substantially shorter in the observation group (Table 2). The total hospital length of stay was also significantly reduced in the observation group (mean difference: −6.5 days; 95% CI: −7.4 to −5.6; $P < 0.001$). All discharge decisions were based on standardized clinical stability criteria, and no patients were transferred to other hospitals or died during the study period, eliminating competing risks for this outcome.

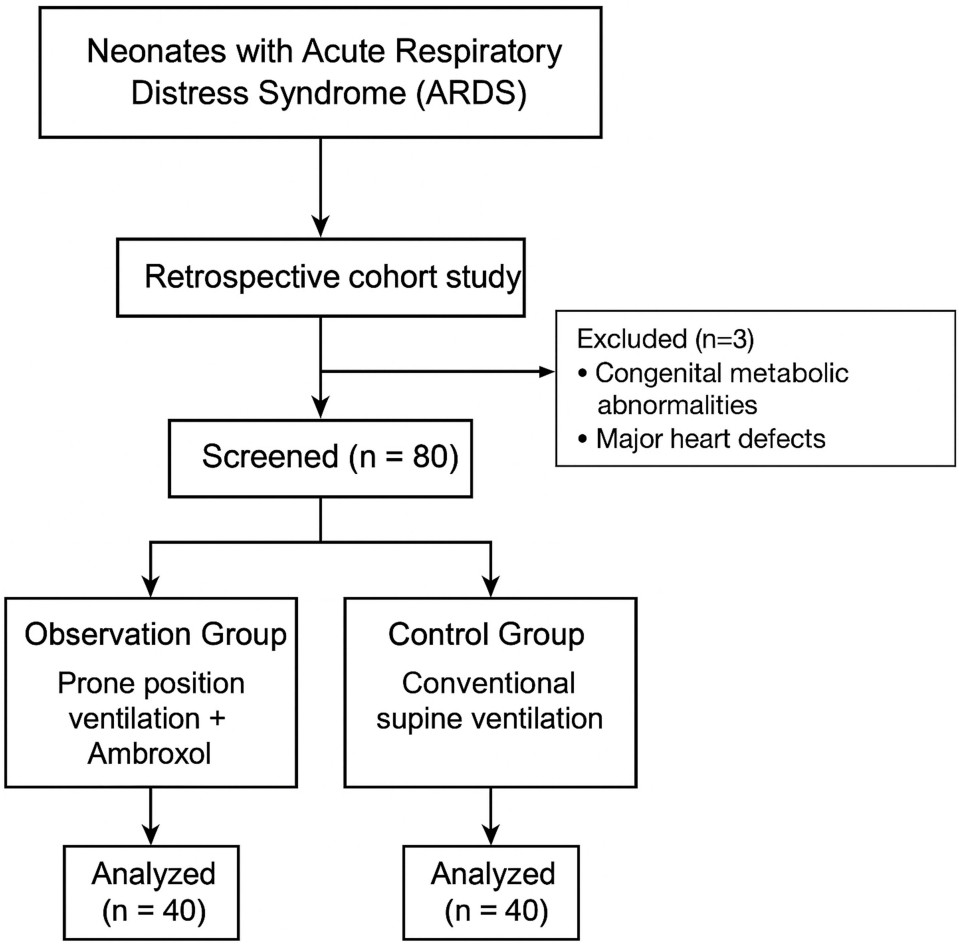

Figure 1 Participant Flow Diagram (STROBE-compliant).

Physiological and Ventilatory Parameters

A linear mixed-effects model, adjusted for baseline values, gestational age, and birth weight, revealed a significantly greater improvement in the Oxygenation Index (OI) over time in the observation group compared to the control group (Group × Time interaction, $P < 0.001$). Post-hoc analyses showed that the observation group had a lower OI at both 24h (T1) and 72h (T2). Similar patterns of greater improvement were observed for pH and $PaCO_2$. Data for all longitudinal physiological parameters are provided in Table 3.

By the third day of treatment, the Peak Inspiratory Pressure (PIP) required to maintain adequate ventilation was significantly lower in the observation group (adjusted mean difference: −1.95 cmH_2O; 95% CI: −2.45 to −1.45; $P < 0.001$), while PEEP and FiO_2 levels were not significantly different between the groups. Hemodynamically, the observation group exhibited significantly lower heart rate and mean arterial pressure at 24 hours post-intervention, suggesting improved cardiopulmonary stability.

Complications and Adverse Events

The overall incidence of major complications was significantly lower in the observation group (12.5% vs. 47.5%; Relative Risk [RR] = 0.26; 95% CI: 0.11 to 0.62; P = 0.001). The raw counts and incidence for each complication are detailed in Table 4. Regarding intervention-specific safety, no episodes of unplanned extubation or central line dislodgement occurred during prone positioning. Two (5.0%) infants in the observation group developed Stage I pressure injuries (redness) on the knees, which resolved with standard nursing care. No adverse events attributable to Ambroxol,

https://doi.org/10.2147/TCRM.S578819

Table 1 Baseline Characteristics and Disease Severity of the Study Population

Characteristic	Control Group (n=40)	Observation Group (n=40)	Statistics	p
Demographics				
Male, n (%)	28 (70.0)	30 (75.0)	χ^2 = 0.244	0.621
Gestational Age, weeks, mean ± SD	32.31 ± 2.27	32.84 ± 2.13	t = −1.077	0.285
Birth Weight, grams, mean ± SD	2987.45 ± 412.33	3012.18 ± 398.76	t = −0.274	0.785
Primary Diagnosis, n (%)			Fisher's Exact Test	0.814
Pneumonia	22 (55.0)	20 (50.0)		
Asphyxia	11 (27.5)	13 (32.5)		
Meconium Aspiration Syndrome	7 (17.5)	7 (17.5)		
Disease Severity at Admission				
Oxygenation Index (OI), mean ± SD	18.5 ± 3.2	19.1 ± 3.5	t = −0.812	0.419
Arterial pH, mean ± SD	7.21 ± 0.08	7.19 ± 0.09	t = 1.067	0.289
$PaCO_2$, mm Hg, mean ± SD	59.8 ± 7.5	61.2 ± 8.1	t = −0.815	0.417
Co-interventions, n (%)				
Received Surfactant	32 (80.0)	34 (85.0)	χ^2 = 0.373	0.541
Received Vasodilators	8 (20.0)	9 (22.5)	χ^2 = 0.082	0.775
Additional Baseline Support				
Duration of Mechanical Ventilation prior to enrollment, days, median [IQR]	1.5 [1.0, 2.0]	1.0 [1.0, 2.0]	Z = −0.891	0.373
Duration of Oxygen Therapy prior to enrollment, days, median [IQR]	2.0 [1.0, 3.0]	*2.0 [1.0, 3.0]*	Z = −0.245	0.806

Table 2 Comparison of Clinical Outcomes Between the Two Groups

Outcome	Control Group (n=40)	Observation Group (n=40)	Effect Size (95% CI)	p
Ventilator-Free Days at Day 28, days, median (IQR)	14 (10–17)	18 (15–21)	-	0.003
Duration of Mechanical Ventilation, days, mean ± SD	9.85 ± 1.25	7.81 ± 1.11	2.04 (1.55 to 2.53)	<0.001
Total Oxygen Therapy, days, mean ± SD	12.01 ± 3.11	8.24 ± 2.97	3.77 (2.42 to 5.12)	<0.001
Hospital Length of Stay, days, mean ± SD	21.66 ± 2.87	15.11 ± 1.38	6.55 (5.61 to 7.49)	<0.001
t-value	2.35			
df	78			

Note: Mann–Whitney *U*-test used for non-normally distributed VFDs.

such as bradycardia, hypotension, gastrointestinal intolerance, or hypersensitivity reactions, were documented in any patient.

Discussion

This retrospective study provides preliminary clinical evidence suggesting that the combined intervention of prone position ventilation and intravenous ambroxol may be associated with improved respiratory outcomes in neonates with ARDS, as indicated by significantly more ventilator-free days, shorter durations of respiratory support, and improved oxygenation parameters compared to conventional supine ventilation.

The primary pathophysiological mechanism of NRDS involves a deficiency in pulmonary surfactant, leading to alveolar collapse and impaired gas exchange.[15–18] The potential benefits observed in the observation group may be explained by the complementary mechanisms of the two interventions. Prone positioning is known to improve thoraco-diaphragmatic synchrony, promote more uniform alveolar ventilation by preferentially expanding dorsal lung regions, and facilitate airway secretion clearance.[19–21] These effects likely contributed to the significantly greater improvement in

Table 3 Longitudinal Changes in Physiological and Ventilatory Parameters

Parameter	Group	T0 (Baseline)	T1 (24 Hours)	T2 (72 hours)	p (Interaction)
Oxygenation Index (OI)					< 0.001
	Control (n=40)	18.50 ± 3.20	14.05 ± 2.85	10.88 ± 2.10	
	Observation (n=40)	19.10 ± 3.50	11.21 ± 2.41	8.54 ± 1.65	
Arterial pH					0.002
	Control (n=40)	7.21 ± 0.08	7.26 ± 0.05	7.31 ± 0.03	
	Observation (n=40)	7.19 ± 0.09	7.31 ± 0.03	7.38 ± 0.04	
$PaCO_2$ (mm Hg)					< 0.001
	Control (n=40)	59.80 ± 7.50	55.56 ± 3.35	50.23 ± 4.18	
	Observation (n=40)	61.20 ± 8.10	53.56 ± 4.05	45.65 ± 2.17	
Peak Inspiratory Pressure (PIP, cmH_2O)					0.015
	Control (n=40)	23.50 ± 1.80	22.01 ± 1.45	21.22 ± 1.11	
	Observation (n=40)	23.80 ± 1.95	20.55 ± 1.30	19.02 ± 1.05	
Positive End-Expiratory Pressure (PEEP, cmH_2O)					0.721
	Control (n=40)	7.02 ± 0.50	6.11 ± 0.40	5.08 ± 0.33	
	Observation (n=40)	7.05 ± 0.55	6.08 ± 0.35	5.11 ± 0.23	
Fraction of Inspired Oxygen (FiO_2, %)					0.455
	Control (n=40)	58.5 ± 5.2	47.3 ± 4.8	39.25 ± 3.25	
	Observation (n=40)	59.2 ± 5.5	45.1 ± 5.1	38.94 ± 4.17	
F-value	4.21				
df	3,78				

Note: P < 0.05 vs. Control group at the same time point, based on post-hoc ANCOVA.
Abbreviations: OI, Oxygenation Index; $PaCO_2$, arterial partial pressure of carbon dioxide.

Table 4 Incidence of Complications and Adverse Events

Complication/Adverse Event	Control Group (n=40) n (%)	Observation Group (n=40) n (%)	Relative Risk (95% CI)
Pneumothorax	4 (10.0)	0 (0.0)	–
Intracranial Hemorrhage (≥Grade II)	9 (22.5)	2 (5.0)	0.22 (0.05 to 0.95)
Ventilator-Associated Pneumonia	6 (15.0)	3 (7.5)	0.50 (0.13 to 1.89)
Any Major Complication	19 (47.5)	5 (12.5)	0.26 (0.11 to 0.62)
Intervention-Related Adverse Events			
Pressure Injury (Stage I)	0 (0.0)	2 (5.0)	-
Unplanned Extubation	0 (0.0)	0 (0.0)	-

the Oxygenation Index (OI) over time and the lower Peak Inspiratory Pressure (PIP) required in the observation group, as our linear mixed-effects model indicated. The reduction in PIP is a particularly meaningful finding, as it suggests that the combined intervention may facilitate lung-protective ventilation by lowering the driving pressure, a key factor in mitigating ventilator-induced lung injury.

Ambroxol hydrochloride, the pharmacological component of the combined therapy, possesses mucolytic and secretagogue properties and is known to stimulate the synthesis and secretion of pulmonary surfactant.[22–25] Its potential anti-inflammatory and antioxidant effects may also contribute to lung protection.[26–30] While our study was not designed to disentangle the individual contributions of proning versus ambroxol, the synergistic action of improved mechanical ventilation (through proning) and enhanced biochemical lung protection (potentially through ambroxol) provides a plausible biological rationale for the observed association with better outcomes. The improved hemodynamic stability

(lower HR and MAP) in the observation group may be an indirect benefit of improved respiratory mechanics and gas exchange, reducing the overall cardiopulmonary stress on the neonates.

Importantly, our findings must be interpreted with considerable caution regarding safety. The combined intervention appeared feasible in our cohort. We documented no serious adverse events directly attributable to the interventions, such as unplanned extubation or line dislodgement during proning. However, the occurrence of Stage I pressure injuries in 5% of prone-positioned infants underscores a known risk that requires vigilant nursing care and skin protection protocols in any unit adopting this strategy. No acute adverse drug reactions to ambroxol were recorded, but the safety profile of intravenous ambroxol in neonates, especially very low birth weight infants, warrants further investigation in larger, prospective studies that are specifically powered to detect rare adverse events.

The significantly lower incidence of major complications, such as intracranial hemorrhage and pneumothorax, in the observation group is a promising signal. This may be related to the more stable respiratory and hemodynamic status, potentially reducing the swings in cerebral blood flow and the need for high-pressure ventilation. However, the non-randomized design prevents us from establishing a causal link, and these findings must be considered hypothesis-generating.

By comparing the latest guidelines and research, it is demonstrated that the results of this study are consistent with current evidence-based medicine evidence, such as the mechanism by which prone position ventilation improves oxygenation, which is consistent with the conclusions of the PROSEVA trial.

Study Limitations and Future Directions

This study has several important limitations that constrain the interpretation of our findings. First, its retrospective and non-randomized nature introduces significant risks of selection bias and unmeasured confounding. Although we attempted to balance key baseline characteristics and severity indices, residual confounding by indication (eg, subtle differences in disease acuity influencing the clinician's decision to use the combined therapy) cannot be ruled out. The subjective component in outcome assessment, particularly for earlier efficacy measures, and the lack of blinding are additional sources of potential bias. Furthermore, the sample size, while sufficient to detect large differences in the primary outcome, was not based on a formal a priori power calculation and is inadequate for definitive conclusions or subgroup analyses.

Therefore, our results should not be construed as practice-changing but rather as a foundation for future research. The promising signals of benefit and acceptable feasibility justify the planning of a robust, prospective randomized controlled trial (RCT). A future RCT should be adequately powered, incorporate blinding of outcome assessors, utilize strictly objective primary endpoints (such as ventilator-free days), and include systematic monitoring of both efficacy and safety outcomes, including long-term neurodevelopmental follow-up. Such a study is essential to definitively determine the efficacy and safety of this combined approach and to establish any causal relationship with the improved outcomes observed here.

Conclusion

In conclusion, this retrospective analysis suggests that prone position ventilation combined with intravenous ambroxol is a feasible intervention that may be associated with short-term respiratory benefits and a lower complication rate in neonates with ARDS. However, the inherent limitations of the study design preclude definitive conclusions regarding causality and generalizability. These findings serve to generate the hypothesis that this combined strategy is beneficial, an hypothesis that now requires rigorous validation in a prospective, randomized controlled setting before any clinical recommendations can be made.

Funding

Science and Technology Plan Project of Quanzhou Science and Technology Bureau (No.:2025QZNY081).

Disclosure

The author declares that this study has not received any financial support or personal interests that may affect the objectivity and interpretation of the results during the writing, research, and publication process.

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