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OUTCOMES OF PRETERM NEONATES WITH RESPIRATORY DISTRESS SYNDROME USING EARLY NON-INVASIVE VENTILATION

Original Research

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ABSTRACT

Background: Premature neonates are highly susceptible to respiratory distress syndrome (RDS), requiring advanced interventions like non-invasive ventilation to manage their condition effectively. This study investigates the application of early continuous positive airway pressure (CPAP) to manage RDS in preterm neonates, focusing on associated outcomes and predictive factors for success or failure of the therapy.

Objective: The objective current study is to assess the frequency of outcomes linked with early non-invasive ventilation in preterm neonates with RDS. Secondary objective is to evaluate the impact of various factors on the success or failure of early non-invasive ventilation in these patients.

Methods: A nested case-control study was conducted at the Department of Pediatrics, Combined Military Hospital, Kharian, from October 2022 to September 2023, involving 75 premature neonates with RDS. Exclusion criteria included neonates requiring intubation at birth or those with major congenital anomalies. All subjects were treated with CPAP and surfactant and monitored for 28 days for the necessity of mechanical ventilation and the emergence of complications.

Results: CPAP therapy failed in 13 (17.3%) neonates. Complications included bronchopulmonary dysplasia in 14 (18.7%) patients, patent ductus arteriosus in 15 (20.0%), air-leak syndromes in 5 (6.7%), and necrotizing enterocolitis in 3 (4.0%). The mortality rate was 17.3%. Neonates born at less than 30 weeks of gestation, those with a low birth weight, or severe RDS showed significantly higher odds of CPAP failure.

Conclusion: Early CPAP provides a critical non-invasive ventilation strategy in the management of RDS in preterm neonates, although it is associated with substantial failure rates and complications. Identifying predictive factors for CPAP outcomes can guide clinical interventions and improve neonatal care.

Keywords: Bronchopulmonary Dysplasia, Early Non-Invasive Ventilation, Necrotizing Enterocolitis, Patent Ductus Arteriosus, Premature Delivery, Respiratory Distress Syndrome, Surfactant Therapy.

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INTRODUCTION

Premature birth significantly impacts neonatal health globally, with an estimated one-fifth of all deliveries in Pakistan resulting in preterm neonates (1). These infants face numerous health challenges, chief among them being respiratory distress syndrome (RDS), which affects about one-third of preterm births in the region (2). RDS arises from a deficiency in surfactant and the immaturity of lung structures, leading to high surface tension in the alveoli and small airways. This condition reduces tissue compliance and leads to atelectasis, ultimately impairing gas exchange (3). The consequences of RDS extend beyond immediate respiratory failure, predisposing neonates to severe complications such as pulmonary infections, intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and significant neurodevelopmental delays, including cerebral palsy (3,4).

Historically, the management of RDS has relied heavily on invasive mechanical ventilation, which, despite its effectiveness, is fraught with risks including barotrauma, air-leak syndromes, and ventilator-associated lung injury, not to mention the complications arising from prolonged intubation (5). In recent years, however, a paradigm shift towards early non-invasive ventilation (NIV) techniques such as continuous positive airway pressure (CPAP) and high-flow nasal cannula (HFNC) therapy has emerged (6,7). These methods aim to deliver essential respiratory support while minimizing the risks associated with mechanical ventilation by avoiding endotracheal intubation (7). Early application of CPAP has been shown to improve lung compliance, decrease the incidence of ventilator-associated complications, and enhance overall neonatal outcomes (8,9).

Despite the advantages, CPAP does not universally prevent the need for mechanical ventilation, with about half of the neonates initially managed with CPAP requiring escalated care due to treatment failure (10). This introduces the necessity to identify and analyze the factors influencing the success or failure of CPAP in treating RDS. Understanding these elements is crucial for developing targeted strategies to optimize outcomes and reduce the morbidity associated with this condition. The objective of this article is to explore the outcomes of early non-invasive ventilation in preterm neonates with RDS, focusing on the effectiveness of CPAP in various clinical settings. It seeks to delineate the factors that contribute to the success or failure of this intervention, providing a foundation for enhancing clinical protocols and improving neonatal care.

METHODS

This nested case-control study was conducted from October 2022 to September 2023 at the Department of Pediatrics, Combined Military Hospital, Kharian. It involved 75 premature neonates diagnosed with respiratory distress syndrome (RDS) who required non-invasive ventilation to maintain adequate gas exchange. Participation was contingent upon obtaining informed consent from the parents or guardians of these neonates. The study adhered strictly to the Declaration of Helsinki and was approved by the institutional ethics committee.

The sample comprised neonates selected through consecutive, non-probability sampling. Sample size determination utilized the OpenEpi calculator, aiming for a 95% confidence level and 95% power, with a case to control ratio of 1. This calculation was based on a population control exposure rate of 88.9% and an odds ratio of 0.028, which reflected the percentage of neonates delivered via cesarean section who successfully underwent non-invasive ventilation (NIV) and the associated odds ratio for NIV success in cesarean-delivered neonates as reported by Handoka et al. (11). Initially calculated at 26, the sample size was increased to 75 to enhance the study's robustness. Inclusion criteria were neonates born between 28 and 34 weeks of gestation exhibiting symptoms of RDS—characterized by tachypnea exceeding 60 breaths per minute, intercostal or subcostal retractions, nasal flaring, and cyanosis, with a required fraction of inspired oxygen (FiO2) greater than 0.3 within the first 30 minutes post-birth (12). Neonates requiring intubation at birth, those with severe respiratory failure prior to enrollment, major congenital anomalies (excluding patent ductus arteriosus), prolonged premature rupture of membranes, or clinical chorioamnionitis were excluded.

Upon enrollment, each participant underwent a thorough initial evaluation documenting relevant pregnancy and delivery characteristics, followed by a clinical examination. The severity of RDS was assessed using the Silverman Andersen Respiratory Severity Score, with scores above 4 indicating severe disease (13). Treatment protocols included immediate CPAP, tailored to individual needs, and surfactant administration at 200 mg/kg initially, followed by up to two additional doses of 100 mg/kg twelve hours apart. Monitoring continued

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for 28 days post-delivery, focusing on the need for mechanical ventilation, defined by critical thresholds in blood gas parameters—and other RDS complications like bronchopulmonary dysplasia, intraventricular hemorrhage, air-leak syndrome, patent ductus arteriosus, necrotizing enterocolitis, and mortality. Data were analyzed using SPSS version 27.0, with quantitative variables such as maternal age, gestational age at birth, birth weight, APGAR score at one minute, time to CPAP initiation, time to surfactant administration, and total CPAP duration presented as means and standard deviations or medians and interquartile ranges. Qualitative variables, including gender, antenatal corticosteroid usage, mode of delivery, and CPAP outcomes were expressed as frequencies and percentages. Normality of distributions was assessed via the Shapiro-Wilk test. Comparative statistical analyses employed the Chi-Square test or Fisher's Exact test for qualitative data and the independent samples t-test or Mann-Whitney U test for quantitative data, with a significance threshold set at $p \leq 0.05$. Odds ratios were calculated for factors associated with CPAP failure to identify predictive indicators of treatment outcomes.

RESULTS

The study was conducted on 75 premature neonates born at our institution over a one-year period. The mothers of these neonates had a median age of 27 years, with an interquartile range of 6 years, and the median gestational age at delivery was 31 weeks, with an interquartile range of 2 weeks. A small proportion of the pregnancies, 5.3%, were multiple gestations. A significant majority, 78.7%, of the pregnancies had received antenatal corticosteroids to enhance fetal lung maturity. The mode of delivery varied, with 65.3% of deliveries conducted per vaginum and 34.7% via cesarean section. Male neonates comprised 60% of the cases. The mean birth weight was 1634.96 grams, with a standard deviation of 395.05 grams, and the median APGAR score at one minute post-birth was 6, with an interquartile range of 3.

Table 1 Patient characteristics at enrollment according to RDS severity (n=75)

Variable	Non-Severe RDS (n=55)	Severe RDS (n=20)	p-value
Maternal Age (years)	29.0 (IQR: 6.0)	25.5 (IQR: 5.0)	0.009
Gestational Age at Birth (weeks)	32.0 (IQR: 2.0)	29.0 (IQR: 2.0)	<0.001
Multiple Gestation	3 (5.5%)	1 (5.0%)	1.00
Antenatal Steroid Use	48 (87.3%)	11 (55.0%)	0.003
Mode of Delivery			
Per Vaginum	36 (65.5%)	13 (65.0%)	0.971
C-Section	19 (34.5%)	7 (35.0%)	
Neonatal Gender			
Male	33 (60.0%)	12 (60.0%)	1.00
Female	22 (40.0%)	8 (40.0%)	
Birth-weight (g)	1831 (IQR: 361)	1199 (IQR: 408)	<0.001
APGAR Score at One Minute	6.0 (IQR: 3.0)	6.0 (IQR: 3.0)	0.130
Time to CPAP (mins)	28.0 (IQR: 15)	20.50 (IQR: 13.0)	0.009
Time to Surfactant (mins)	39.0 (IQR: 19.0)	41.5 (IQR: 17.0)	0.189

The study stratified the neonates based on the severity of RDS: 26.7% were classified as having severe RDS, while the remaining 73.3% were classified as non-severe. The initiation of CPAP treatment was swift, occurring at a median of 24 minutes post-delivery, and surfactant therapy followed at a median of 41 minutes. The maternal age was statistically significantly younger in the severe RDS group

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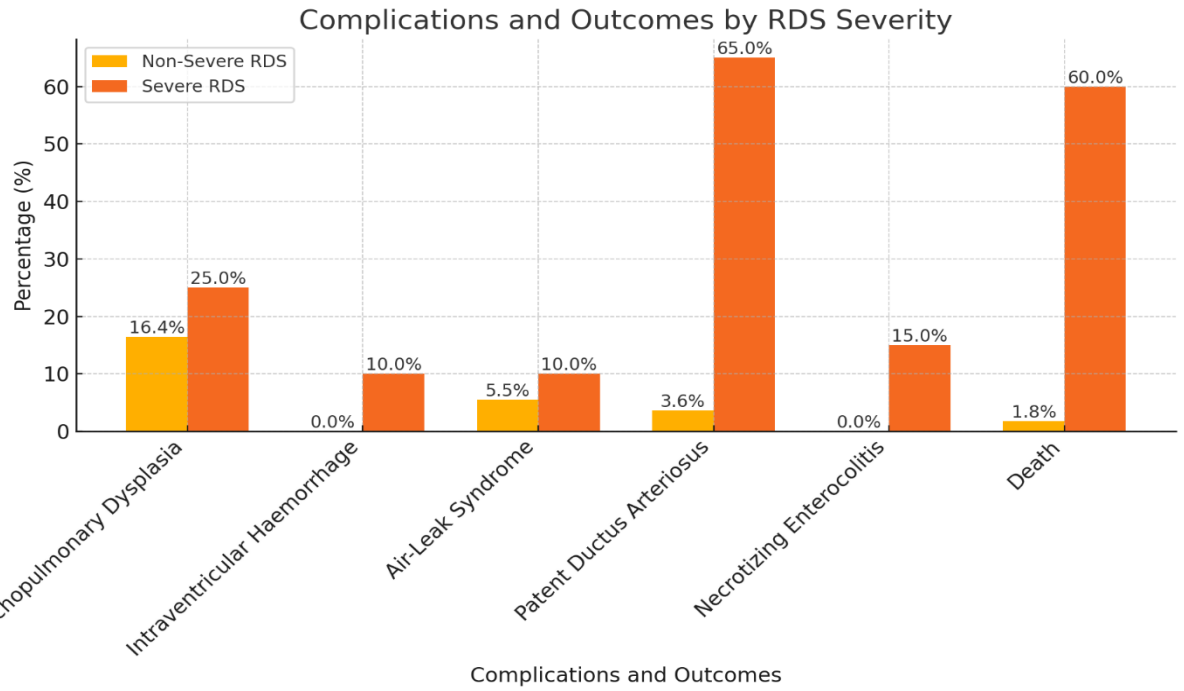
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compared to the non-severe group. Similarly, the gestational age at birth was significantly lower in the severe group, indicating a correlation between earlier gestational delivery and increased severity of RDS.

Table 2 Study Outcomes according to RDS severity (n=75)

Variable	Non-Severe RDS (n=55)	Severe RDS (n=20)	p-value
Duration of CPAP (hours)	72.0 (IQR: 116.0)	85.0 (IQR: 115.0)	0.155
Failure of CPAP	1.0 (1.8%)	12.0 (60%)	<0.001
Complications			
Bronchopulmonary Dysplasia	9 (16.4%)	5 (25.0%)	0.396
Intraventricular Haemorrhage	-	2 (10.0%)	0.068
Air-Leak Syndrome	3 (5.5%)	2 (10.0%)	0.485
Patent Ductus Arteriosus	2 (3.6%)	13 (65.0%)	<0.001
Necrotizing Enterocolitis	-	3 (15.0%)	0.003
Death	1.0 (1.8%)	12.0 (60.0%)	<0.001

The study outcomes were revealing with regard to the efficacy of CPAP treatment and its complications. The overall failure rate of CPAP was 17.3%, with a significantly higher failure rate observed in the severe RDS group. This group also had a higher incidence of patent ductus arteriosus and was more likely to develop necrotizing enterocolitis. Intraventricular hemorrhage and death were notably higher in the severe RDS group as well. The median duration of CPAP was 80 hours, with a wide interquartile range, reflecting the variability in treatment duration based on individual patient needs and responses.



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Table 3 Odds ratio of different variables in the development of CPAP failure (n=75)

Variable	Odds Ratio, p-value
Maternal Age < 27 years	2.91 (CI 95% 0.85 – 9.98), p=0.081
Gestational Age < 30 weeks	43.21 (CI 95% 7.90 – 236.45), p<0.001
Multiple Gestation	1.22 (CI 95% 1.09 – 1.37), p=0.347
Antenatal Steroid Use	0.22 (CI 95% 0.06 – 0.81), p=0.016
Vaginal Delivery	1.97 (CI 95% 0.49 – 7.89), p=0.334
Neonatal Gender	0.74 (CI 95% 0.22 – 2.46), p=0.618
Birth-weight <1500 g	1.87 (CI 95% 1.32 – 2.64), p<0.001
APGAR Score at One minute	2.11 (CI 95% 0.53 – 8.43), p=0.286
RDS Severity	81.00 (CI 95% 9.24 – 710.06), p<0.001
Time to CPAP >30 minutes	3.97 (CI 95% 0.81 – 19.46), p=0.072
Time to Surfactant >45 minutes	0.94 (CI 95% 0.28 – 3.23), p=0.926

A further analysis to determine the odds ratios for various factors influencing CPAP failure highlighted several significant predictors. Gestational age less than 30 weeks and low birth weight were both associated with a higher likelihood of CPAP failure, while antenatal steroid use appeared to be protective, significantly decreasing the odds of CPAP failure. Severe RDS was strongly predictive of CPAP failure, underscoring the challenge of managing more severely affected neonates with non-invasive techniques alone. These results underscore the complexities of managing RDS in premature neonates with CPAP, revealing both the potential and limitations of non-invasive respiratory support in this vulnerable population. The significant correlations between patient characteristics and treatment outcomes provide valuable insights for clinical practice, particularly for anticipating and mitigating the risks of CPAP failure.

DISCUSSION

Our study elucidates the outcomes and complications associated with continuous positive airway pressure (CPAP) therapy in premature neonates with respiratory distress syndrome (RDS), highlighting several predictors of poor CPAP response. Approximately one-fifth of the neonates in our study failed CPAP therapy, a figure that aligns closely with that reported by Gulczyńska et al., who observed a 27.0% failure rate (15). In contrast, studies by Abdullah et al. and Dargaville et al. reported higher failure rates of 37.4% and 43.0%, respectively (16,17). The variation in CPAP failure rates across these studies can largely be attributed to differences in the populations examined, particularly gestational age at birth, which influences lung maturity and subsequently, the risk of CPAP failure.

Patent ductus arteriosus (PDA) and bronchopulmonary dysplasia (BPD) were the most common complications in our cohort, occurring in about 20% of the patients. These findings are in line with Walsh et al., who reported similar rates of PDA and BPD among neonates born after 28 weeks of gestation (18). However, our study noted lower incidences of necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH) compared to those found in populations comprising younger preterm neonates, suggesting that gestational age may play a critical role in the prevalence of these complications.

Significantly, our data revealed that neonates born under 30 weeks of gestation were at a markedly higher risk of CPAP failure, with an odds ratio (OR) indicating a substantial increase (OR: 43.21; CI 95% 7.90 – 236.45, p<0.001). This finding is supported by the study from Tourneux et al., which documented a decrease in CPAP failure risk with each additional week of gestational age (19). However, Abdallah et al. did not find significant differences in CPAP failure rates between neonates born before and after 30 weeks, potentially due to a majority of their study population being extremely preterm (16).

Low birth weight was another significant predictor of CPAP failure. Our results, indicating an increased risk with birth weights under 1500 g (OR: 1.87; CI 95% 1.32 – 2.64, p<0.001), are corroborated by findings from Gulczyńska et al., who noted each 100 g increase

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in birth weight decreased the risk of CPAP failure (15). Permatahati et al. also reported a markedly higher risk for neonates under 1000 g (20).

Interestingly, while severe RDS significantly increased the risk of CPAP failure (OR: 81.00; CI 95% 9.24 – 710.06, p<0.001), our study identified antenatal steroid use as a protective factor, reducing the likelihood of CPAP failure (OR: 0.22; CI 95% 0.06 – 0.81, p=0.016). This contrasts with other studies where antenatal corticosteroid therapy did not demonstrate a reduction in CPAP failure risk (15,16,19-21), a discrepancy that may stem from differences in study populations, particularly regarding the prevalence of extremely preterm neonates.

The strength of our study lies in its focus on a specific gestational age range, allowing for a more controlled examination of CPAP outcomes and complications. However, this specificity also constitutes a limitation, as it restricts the generalizability of our findings to broader preterm populations. Further, while the study benefits from a robust sample size for statistical analysis, the observational nature of the design may introduce biases related to unmeasured confounders.

In conclusion, our study contributes to the understanding of CPAP therapy in managing RDS in premature neonates, offering insights into the factors that influence therapy outcomes. These findings are instrumental in guiding clinical decisions and optimizing treatment strategies for this vulnerable patient population. Future research should aim to explore the effects of CPAP in a more diverse preterm population to enhance the applicability of these outcomes across different clinical settings.

CONCLUSION

Continuous positive airway pressure (CPAP) represents a vital non-invasive ventilation (NIV) strategy that offers a less invasive alternative to mechanical ventilation for managing respiratory distress syndrome in preterm neonates. While CPAP is effective and avoids the complications inherent to more invasive methods, it does carry a notable risk of failure and is associated with various complications that could impact neonatal outcomes. The emergence of alternative NIV techniques may potentially enhance treatment efficacy, highlighting an area ripe for future research. Additionally, our findings underscore the critical roles of birth weight and antenatal corticosteroid administration in predicting CPAP success. These insights are crucial for clinicians to identify at-risk neonates early and implement targeted interventions promptly, improving the overall management and outcomes of premature infants.

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