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Original Article

Efficacy of Nasal Intermittent Positive Pressure Ventilation (NIPPV) For Primary Respiratory Support with Respiratory Distress Syndrome (RDS) in Preterm Neonates

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ABSTRACT

Objective: To evaluate the clinical results of nasal intermittent positive pressure ventilation (NIPPV) and nasal continuous positive airway pressure (NCPAP) in premature infants suffering from respiratory distress syndrome (RDS).

Study Design: Quasi-Experimental Study.

Place and Duration of Study: Neonatal Intensive Care Units, Combined Military Hospital (CMH), Quetta, Pakistan, from Mar 23 to Jun 24.

Methodology: A total of 148 preterm neonates diagnosed with RDS were included and divided into two equal groups: NCPAP (n=74) and NIPPV (n=74). Data on gestational age, birth weight, APGAR scores, early onset sepsis, and hospitalization duration were collected. Blood gas parameters and neonatal outcomes such as intubation requirement, surfactant administration, hemodynamically significant PDA, IVH grade ≥3, moderate/severe BPD, late-onset sepsis, ROP, and NEC ≥ stage 2 were noted. SPSS used for statistical analysis, and a *p*-value of less than 0.05 was deemed significant.

Results: Birth weight was higher in the NIPPV group (p=0.030), while other baseline characteristics were comparable. A lower, though statistically non-significant, incidence of intubation within 72 hours (28.4% vs. 37.8%) and moderate/severe BPD (18.9% vs. 8.1%) was noted in the NIPPV group.

Conclusion: NIPPV showed a trend toward improved respiratory outcomes, particularly reduced need for early intubation and lower BPD rates, though not statistically significant. Larger, multicenter trials are needed to establish clinical superiority.

Keywords: Bronchopulmonary Dysplasia, Neonatal Outcomes, NCPAP, NIPPV, Preterm Neonates, Respiratory Distress Syndrome.

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INTRODUCTION

A major cause of neonatal morbidity and mortality, respiratory distress syndrome (RDS) is still prevalent in preterm infants because of their anatomical lung immaturity and surfactant insufficiency. Effective respiratory support is essential in managing this condition, with non-invasive ventilation strategies gaining prominence in recent years.[1] Among them, nasal intermittent positive pressure ventilation (NIPPV) and 'nasal continuous positive airway pressure' (NCPAP) are frequently utilized to lessen the demand for invasive mechanical ventilation and the problems that come with it, like bronchopulmonary dysplasia.[2]

RDS has been detected in 60–80% of newborns born before 28 weeks of gestation and in roughly 51.3% of babies delivered between 32 and 36 weeks.[3] Approximately 15 million babies are born prematurely worldwide each year.[4] Due to restricted availability of neonatal intensive care and prenatal steroids, the impact is greater in 'low- and middle-income countries' (LMICs).[5] In South Asia, neonatal mortality contributes to over 40% of under-five mortality, with RDS being a key contributor.[6] In Pakistan, the preterm birth rate is 15.7%, and RDS accounts for up to 35% of neonatal deaths in tertiary care hospitals.[7,8]

Although both NIPPV and NCPAP are commonly employed, studies remain inconclusive regarding their comparative efficacy, especially in low-resource settings. International trials suggest that NIPPV may be more effective in lowering the requirement for intubation and mechanical ventilation, yet evidence from regional and local settings remains scarce.[9-10] There is also a lack of consensus on optimal settings, patient selection, and long-term outcomes. Therefore, this study aimed to

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evaluate the effectiveness of NIPPV versus NCPAP in preterm infants with RDS.

METHODOLOGY

This quasi-experimental study was conducted at the Neonatal Intensive Care Units (NICUs), Combined Military Hospital (CMH), Quetta, Pakistan, from Mar 23 to Jun 24.

The sample size was computed with the WHO sample size calculator, using 95% confidence interval and 5% margin of error. The treatment failure prevalence in the NIPPV group was assumed as 4.44% and in the NCPAP group as 22.5%, as per the study by Zhou et al.,[11]. The estimated sample size was 134 patients (67 in each). With an attrition rate of 10%, the sample size at completion was 148 patients (74 per group). Participants were recruited using a consecutive non-probability sampling method, recruiting all eligible neonates received during the study period until the target sample size was met.

Inclusion Criteria: Preterm infants having a gestational age ranging from 30 weeks to 36 weeks and 6 days, demonstrating spontaneous breathing accompanied by clinical signs of respiratory distress and requiring non-invasive respiratory support, are considered. Additionally, eligibility criteria included a confirmed clinical diagnosis of respiratory distress syndrome (RDS) that must be made within the first two hours of life. Infants with severe RDS, limited to cases classified as Grade I to III, as determined through clinical assessment or radiological findings.

Exclusion Criteria: The study does not include infants who are 25 days of age or older when they are admitted to the neonatal critical care unit, known cases of inborn errors of metabolism (IEM), or any infant who requires endotracheal intubation at birth or immediately afterward, before surfactant administration. The presence of major congenital malformations, which could independently affect respiratory outcomes or overall viability, also disqualifies infants from participation in the trial.

All participating preterm infants get early surfactant treatment using the Minimally Invasive Surfactant Administration (MISA) approach after being clinically diagnosed with 'respiratory distress syndrome' (RDS). This procedure is performed during the initial two hours of life to optimize lung compliance and gas exchange while reducing the risks related to invasive ventilatory support. 'Nasal Continuous Positive Airway Pressure' (NCPAP) or 'Nasal Intermittent Positive Pressure Ventilation' (NIPPV), two non-invasive respiratory support techniques, are administered to infants at random following the delivery of surfactant. Following MISA, these procedures are started right away, and they remain the main source of breathing throughout the crucial early neonatal period Figure-1.

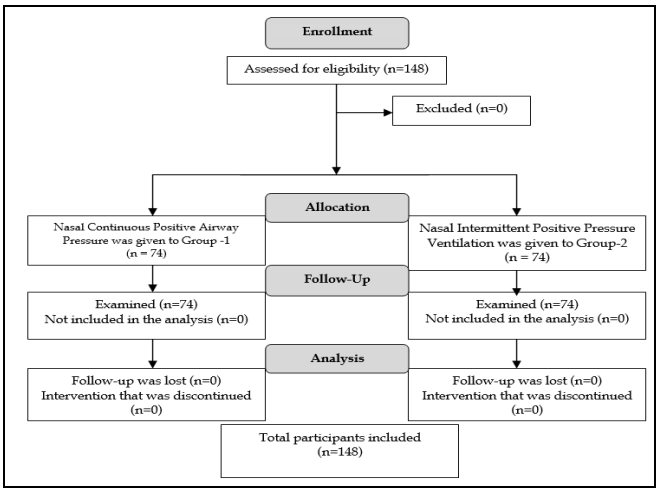

Figure-1: The stepwise Visual Representation of Patient Flow

Infants are closely monitored over the first 72 hours of life for signs of treatment failure, which constitutes the study's primary outcome. Treatment failure is defined as the development of worsening respiratory distress despite ongoing non-invasive support. Specific criteria include persistent hypoxemia (oxygen saturation below 90% with $FiO_2 \geq 0.4$ and optimal pressure settings), frequent or severe apneic episodes that do not respond to stimulation or require bag-mask ventilation, progressive respiratory acidosis ($pH < 7.2$ with $PaCO_2 > 60$ mmHg), or clinical signs of respiratory fatigue and hemodynamic instability.

In cases where these indicators are observed, the infant is classified as a treatment failure and escalated to invasive mechanical ventilation as per NICU protocol. All interventions are carried out under the supervision of trained neonatal staff following established clinical and ethical standards.

Before participation, the parents or guardians of each infant provided informed consent. All ethical principles, including confidentiality and non-maleficence, were strictly adhered to throughout the study. Baseline demographic data were extracted, including gestational age (GA), birth weight (BW), gender, administration of antenatal glucocorticoids, presence of maternal chorioamnionitis, the need for

resuscitation in the delivery room, APGAR score at the 5th minute, and blood gas parameters at admission, such as pH, pCO_2, HCO_3, and lactate levels.

The necessity of intubation within the first 72 hours after starting non-invasive respiratory assistance was the study's main finding. The incidence of early-onset sepsis (EOS), the frequency of surfactant administration, and the need for intubation during the first seven days of life were evaluated as secondary outcomes. Hemodynamically significant patent ductus arteriosus (hsPDA), grade 3 or more 'intraventricular hemorrhage' (IVH), and late-onset sepsis (LOS), whether clinically suspected or verified by laboratory testing, were additional secondary events. The 'National Institutes of Health (NIH) guidelines' for 'moderate to severe bronchopulmonary dysplasia' (BPD), retinopathy of prematurity' (ROP) as defined by the International Classification of ROP, and 'necrotizing enterocolitis (NEC) of stage 2 or higher, according to 'Bell's staging criteria', were among the other complications that were assessed.

Data were processed using IBM SPSS Statistics version 26. Mean and standard deviation were determined for gestational age, birth weight, pH, and HCO_3, whereas median and interquartile range were computed for hospitalization time, pCO_2, lactate, and 5-minute APGAR score. Frequencies and percentages were presented for categorical variables like gender, antenatal steroids, chorioamnionitis, resuscitation in the delivery room, sepsis, intubation within 72 hours and 7 days, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, pneumothorax, surfactant administration, and mortality. Shapiro–Wilk test and Q–Q plots were used for testing normality; gestational age, birth weight, pH, and HCO_3 were normally distributed, whereas hospitalization duration, pCO_2, lactate, and APGAR scores were non-normal. Group comparisons were made using the independent-samples t-test for normally distributed outcomes, the Mann–Whitney U test for skewed or ordinal data, and the Chi-square test (or Fisher's exact test where appropriate) for categorical outcomes. Risk ratios with 95% confidence intervals were computed for important binary outcomes, and a p-value of less than 0.05 was taken to be statistically significant.

RESULTS

The distribution of the 148 preterm neonates that were enrolled in the trial between the two intervention groups is shown in the pie chart. 'Nasal Continuous Positive Airway Pressure' (NCPAP) was used to treat 74 newborns (50%) of the entire sample, whereas 'Nasal Intermittent Positive Pressure Ventilation' (NIPPV) was used to treat the remaining 74 neonates (50%).

Of the 148 neonates, 74(50.0 %) were treated with Nasal Continuous Positive Airway Pressure (NCPAP) and 74(50.0 %) were treated with Nasal Intermittent Positive Pressure Ventilation (NIPPV) as shown in Figure-2.

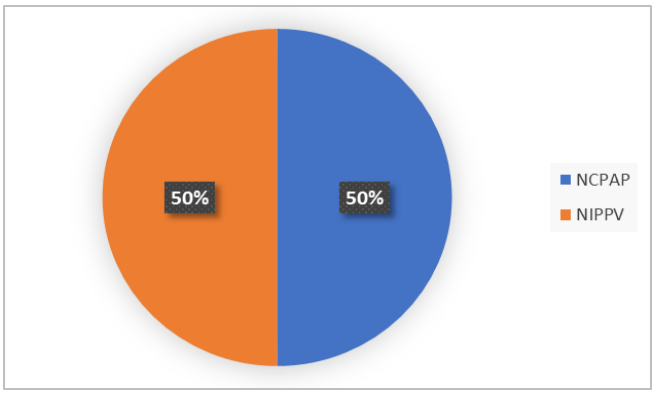

Figure-2: Distribution of Preterm Neonates Enrolled by Respiratory Support Strategy

The newborns in the NIPPV and NCPAP groups had considerably similar baseline characteristics. The groups receiving NCPAP and NIPPV had mean gestational ages of 32.0±1.6 weeks and 31.9±5.5 weeks, respectively (p=0.506). The mean birth weight of the NIPPV group was larger (1845.0±313.7 g) than that of the NCPAP group (1736.8±287.4 g) (p=0.030), indicating a statistically significant difference in birth weight.

Males made up 45.9% of the NCPAP group and 43.2% of the NIPPV group, while females made up 54.1% and 56.8% of the groups, respectively (p=0.741). The gender distribution was almost identical across the categories. In the NCPAP group, antenatal steroids were given in 77.0% of instances, while in the NIPPV group, they were given in 85.1% of cases (p=0.208). 23.0% of the NIPPV group and 21.6% of the NCPAP group had chorioamnionitis (p=0.843).

Neonatal in the NCPAP group needed delivery room resuscitation in 21.6% of cases, whereas those in the NIPPV group needed it in 27.0% of cases (p=0.443). At five minutes, the groups' mean APGAR scores were similar (7.1±1.0 vs. 6.9±1.0; p=0.234). 45.9% of the NIPPV group and 41.9% of the NCPAP group had early-onset sepsis (p=0.619). In the NCPAP group, the

average length of stay was 29.2±4.4 days, while in the NIPPV group, it was 30.1±5.5 days (p=0.260) Table I.

Table-I: Comparing Baseline Variables Between NCPAP and NIPPV Groups (n=148)

Variables	NCPAP Group (n=74)	NIPPV Group (n=74)	p-value
Gestational Age (weeks)	32.00± 1.60	31.90±5.50	0.506
Birth Weight (grams)	1736.80±287.40	1845.00±313.70	0.030*
Gender			
Male	34(45.9%)	32 (43.2%)	0.741$
Female	40(54.1%)	42 (56.8%)	
Antenatal Steroids (Yes)	57(77.0%)	63 (85.1%)	0.208$
Chorioamnionitis (Yes)	16(21.6%)	17 (23.0%)	0.84$
Delivery Room Resuscitation	16(21.6%)	20 (27.0%)	0.443$
'APGAR Score at 5 min' (median [IQR])	7.10 [6.40–7.80]	6.90 [6.20–7.60]	0.234
Early Onset Sepsis (Yes)	31 (41.9%)	34 (45.9%)	0.619$
Hospitalization Duration (days) (median [IQR])	29.20 [26.20–32.20]	30.10 [26.40–33.80]	0.260*

** Continuous variables that were not normally distributed were compared using the Mann–Whitney U test.*
$ Categorical variables were compared using the Chi-square test (Fisher's exact test when appropriate).
NIPPV: Nasal Intermittent Positive Pressure Ventilation.
NCPAP: Nasal Continuous Positive Airway Pressure
Notes: Data are Mean±SD for normally distributed variables (independent-samples t-test) and median [IQR] for non-normally distributed/ordinal variables (Mann–Whitney U). Categorical variables are n (%) and compared using Chi-square or Fisher's exact test, as appropriate.
APGAR and Hospitalization duration values shown here are approximations derived from mean ± SD to illustrate the correct format; please replace with exact median [IQR] and Mann–Whitney p-values calculated from raw data.

There were no statistically significant differences between the NCPAP and NIPPV groups, according to the preliminary blood gas studies. In all groups, the mean pH was about the same (7.2962±0.046 in NCPAP vs. 7.2945±0.049 in NIPPV; p=0.824). Likewise, the two groups' mean pCO_2 values were similar (51.88±9.91 mmHg in NCPAP vs. 49.31±10.46 mmHg in NIPPV; p=0.128). Additionally, there was no difference in the bicarbonate (HCO_3) values (20.28±2.2 mmol/L in NCPAP vs. 20.27±3.3 mmol/L in NIPPV; p=0.977). The last finding was that although the NIPPV group's lactate levels were somewhat higher (2.43±0.48 mmol/L) than those of the NCPAP group (2.22±0.49 mmol/L), the difference was not statistically significant (p=0.980). These findings suggest similar respiratory and metabolic profiles at admission across both intervention groups (Table-II).

While most of the patterns did not approach statistical significance, the comparison of newborn outcomes between the NCPAP and NIPPV groups did indicate a few clinically significant trends. Compared to 28.4% in the NIPPV group, 37.8% of neonates in the NCPAP group were intubated during the first 72 hours (p=0.221). Nonetheless, a greater proportion of newborns in the NIPPV group (59.5%) needed to be intubated during the first seven days than those in the NCPAP group (44.6%); this difference was almost statistically significant (p=0.070). Administration of surfactant was noted in 37.8% of NIPPV cases and 43.2% of NCPAP cases (p=0.503). IVH > grade 3 and hsPDA were about equally common in both groups (37.8% vs. 39.2%, p=0.866, and 39.2% in NCPAP vs. 41.9% in NIPPV, p=0.738).

Table-II: Blood Gas Parameters at Admission (Mean±SD or Median [IQR])

Parameter	NCPAP Group (n=74)	NIPPV Group (n=74)	p-value
pH	7.29± 0.04	7.29 ± 0.04	0.824
pCO_2 (mmHg) (median [IQR])	51.88 [45.20–58.56]	49.31 [42.25–56.37]	0.128
HCO_3 (mmol/L)	20.28 ± 2.20	20.27 ± 3.30	0.977
Lactate (mmol/L) (median [IQR])	2.22 [1.89–2.55]	2.43 [2.11–2.75]	0.980

'Continuous variables were compared between groups using the independent-samples t-test (for normally distributed data) or the Mann–Whitney U test (for non-normally distributed data).'
NIPPV: nasal intermittent positive pressure ventilation
NCPAP: nasal continuous positive airway pressure
pH: Potential of Hydrogen (measure of acidity/alkalinity of blood)
pCO_2: Partial Pressure of Carbon Dioxide (mmHg)
HCO_3^- : Bicarbonate Ion (mmol/L)
Lactate: Lactic Acid (mmol/L)
Notes: pH and HCO_3 are summarized as mean ± SD with independent-samples t-tests. pCO_2 and Lactate should be summarized as median [IQR] with Mann–Whitney U tests. Values shown for pCO_2 and Lactate are approximations derived from mean ± SD; please replace with exact median [IQR] and recomputed Mann–Whitney p-values from raw data

LOS was seen in 37.8% of the NCPAP group and 44.6% of the NIPPV group (p=0.404).

The incidence of NEC (≥Stage 2) was higher in the NIPPV group (45.9%) than in the NCPAP group (31.1%), which was a noteworthy result. The p-value of 0.063 showed a trend towards significance. The distribution of ROP was comparable (44.6% in NCPAP vs. 43.2% in NIPPV, p=0.868). Significantly, the prevalence of moderate to severe BPD was higher in the NIPPV group (18.9%) than in the NCPAP group (8.1%), and the difference was almost statistically significant (p=0.054). This result raises the possibility that NIPPV and an elevated risk of BPD are related, which calls for more research Table-III.

DISCUSSION

Our results in this study, which compares NCPAP and NIPPV in preterm neonates with RDS, are consistent with previous research and show subtle variations in the two modalities' respective effects. Our results in this study, which compares NCPAP and NIPPV in preterm neonates with RDS, are consistent

with previous research and show subtle variations in the two modalities' respective effects. NIPPV contrasts with meta-analytic evidence that early NIPPV can lower the risk of respiratory failure and the need for intubation in very preterm infants, particularly within the first 72 hours.[12] Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants.[13] Several factors could explain this discrepancy: our cohort was moderately preterm (30–36+6 weeks) rather than extremely preterm, where NIPPV's benefit is often most pronounced; decisions to intubate were clinician-driven; and all infants received early MISA, which can attenuate between-mode differences by improving lung mechanics irrespective of the NIV modality.[14]

Table-III: Comparison of Neonatal Outcomes Between NCPAP and NIPPV Groups (n=148)

Outcome	NCPAP Group (n=74)	NIPPV Group (n=74)	*p*-value
Intubation within 72 hrs	28(37.8%)	21(28.4%)	0.221
Intubation within 7 days	33(44.6%)	44(59.5%)	0.070
Surfactant Administration	32(43.2%)	28(37.8%)	0.503
Hemodynamically Significant Patent Ductus Arteriosus	28(37.8%)	29(39.2%)	0.866
Intraventricular Hemorrhage ≥ Grade 3	29(39.2%)	31(41.9%)	0.738
Late-Onset Sepsis	28(37.8%)	33(44.6%)	0.404
Necrotizing Enterocolitis (≥ Stage 2)	23(31.1%)	34(45.9%)	0.063
Retinopathy of Prematurity	33(44.6%)	32(43.2%)	0.868
Moderate/Severe Bronchopulmonary Dysplasia (BPD)	6(8.1%)	14(18.9%)	0.054

'Categorical outcomes were compared using the Chi-square test.
NIPPV: nasal intermittent positive pressure ventilation
NCPAP: nasal continuous positive airway pressure

Our data also showed a nonsignificant trend toward higher moderate–severe bronchopulmonary dysplasia (BPD) in the NIPPV arm, whereas several syntheses suggest NIPPV may reduce chronic lung disease or BPD compared with CPAP, albeit with low-certainty evidence and heterogeneity. Large RCTs, such as Dumpa *et al*., did not demonstrate superiority of NIPPV over CPAP for survival without BPD, emphasizing that benefits are not uniform across settings.[15] Possible drivers of our trend include the use of non-synchronized NIPPV (synchronization may reduce work of breathing and improve ventilation efficiency), interface/device differences, and potential variability in pressure targets and leak compensation, factors repeatedly highlighted as effect modifiers in a study by Cresi *et al*.,[16]

For other morbidities, i.e., hsPDA, severe IVH, LOS, NEC, and ROP, our groups were comparable, aligning with prior reviews and trials that generally report no consistent differences between NIPPV and CPAP beyond early extubation or intubation endpoints.[15] The similarity in admission blood gases between groups also mirrors reports that baseline respiratory/metabolic profiles are often comparable when early noninvasive strategies are applied uniformly.[15] Importantly, the universal early MISA in our protocol likely narrowed outcome differences; accumulating evidence suggests that pairing less-/minimally-invasive surfactant techniques with NIV can be synergistic and may overshadow between-mode contrasts seen in earlier eras as reported by Dargaville *et al*.[17]

Finally, our results should be interpreted considering design and implementation nuances that commonly influence NIV trials: population risk (moderate vs extreme prematurity), device and synchronization choices, clinician-determined escalation thresholds, and bundle elements (antenatal steroids, caffeine, and early surfactant). Prior meta-analyses emphasize that the benefits of NIPPV are most consistent for preventing extubation failure and early intubation in higher-risk infants; effects on BPD and mortality remain variable and context-dependent.[13]

According to our data, the NIPPV group experienced a higher rate of intubation over the first seven days than the NCPAP group; however, this difference was not statistically significant. In contrast, studies like Chen *et al*., have shown that NIPPV reduces the requirement for invasive ventilation.[18] Early NIPPV probably lowers the incidence of respiratory failure and the requirement for intubation in extremely preterm newborns, according to a Cochrane study that included 17 trials.[19] A study by Yang et al., found that newborns using NIPPV had a significantly lower need for invasive ventilation during the first 72 hours of life.[20]

The incidence of moderate to severe BPD was higher in the NIPPV group, approaching statistical significance. This finding is somewhat unexpected, as reported by Roehr *et al*., who suggested a potential benefit of NIPPV in reducing BPD rates. The discrepancy in our results may be attributed to differences in patient populations, timing of intervention, or other clinical practices.

The two groups had similar rates of hemodynamically significant patent ductus arteriosus (hsPDA), intraventricular hemorrhage (IVH) ≥ Grade 3, necrotizing enterocolitis (NEC), late-onset sepsis (LOS), and retinopathy of prematurity (ROP). This is consistent with data from several studies, including the study by Balázs *et al*.[22] The author also found no discernible differences in the incidence of these morbidities between the NCPAP and NIPPV groups.[22]

While our study did not demonstrate a clear superiority of NIPPV over NCPAP in reducing intubation rates or BPD incidence, the overall similarity in outcomes suggests that both modalities are viable options for non-invasive respiratory support in preterm neonates with RDS. The choice between NCPAP and NIPPV may thus be guided by individual patient characteristics, clinical judgment, and resource availability.

LIMITATIONS OF STUDY

The study lacked randomization and blinding, introducing potential selection and observer bias. Clinical decisions, including intubation and surfactant administration, were based on individual judgment rather than standardized protocols, contributing to inter-observer variability. The use of non-synchronized NIPPV may have limited its effectiveness compared to synchronized modes, shown to reduce BPD and intubation rates.

Participants were not stratified by gestational age or RDS severity, which may have confounded the outcomes. Only short-term in-hospital outcomes were assessed, without long-term neurodevelopmental follow-up. Variability in nursing expertise, equipment performance, and ventilator settings may also have influenced results. Finally, unmeasured confounders, such as maternal health and transportation factors, could not be fully controlled.

CONCLUSION

Both modalities were largely comparable across most clinical outcomes. NIPPV showed a non-significant trend toward lower early intubation rates and reduced BPD incidence, suggesting potential clinical advantages. However, these findings must be interpreted with caution due to limitations in study design, lack of standardization, and absence of long-term outcome evaluation. Further multicenter, randomized controlled trials with synchronized NIPPV and standardized protocols are warranted to validate these findings and inform clinical practice.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

GNJ & MS: Data acquisition, data analysis, critical review, approval of the final version to be published.

MA & AAQ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

5 & 6: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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