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RESEARCH

Comparative efficacy of non-invasive ventilation methods in managing neonatal pneumonia: a clinical outcome study

Yenidoğan pnömonisinin yönetiminde non-invaziv ventilasyon yöntemlerinin karşılaştırmalı etkinliği: bir klinik sonlanım çalışması

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Abstract

Purpose: The aim of this study was was to compare the effectiveness and outcomes of non-invasive ventilation (NIV) methods in neonates diagnosed with lower respiratory tract infections (LRTI).

Materials and Methods: A prospective study was conducted in neonates with LRTI treated with high-flow nasal cannula (HFNC), nasal continuous positive airway pressure (NCPAP), or nasal intermittent positive pressure ventilation (NIPPV) in the neonatal intensive care unit. Method failure was defined as switching to another NIV method within 6 hours based on clinical and laboratory findings. The groups were compared for clinical and laboratory findings, length of hospital stay, outcomes, success rates, and complications.

Results: One hundred and six neonates were included with a median gestational age of 38 weeks and birth weight of 2991±673 g. Downes scores at admission were significantly higher in the NCPAP group than in the others. The HFNC group had better of blood pH and CO_2 levels but had a higher rate of treatment failure. NCPAP was associated with the highest success rate (86.8%), followed by NIPPV (78.7%) and HFNC (52.4%). The length of hospital stay was shorter in patients successfully treated with NCPAP and NIPPV. According to the logistic regression analysis, NIPPV significantly reduced the risk of failure compared to HFNC.

Conclusion: NIPPV and NCPAP were more effective than HFNC in the management of neonatal LRTI with shorter hospital stay. HFNC may be effective in stabilizing baseline respiratory parameters in the management of neonatal LRTI.

Keywords:. High-flow nasal cannula, lower respiratory tract infection, nasal CPAP, nasal IPPV, newborn, non-invasive ventilation.

Öz

Amaç: Bu çalışmada alt solunum yolu enfeksiyonu (ASYE) tanısı konulan yenidoğanlarda noninvaziv ventilasyon (NMV) yöntemlerinin etkinliğini ve sonuçlarını karşılaştırmayı amaçladık.

Gereç ve Yöntem: Yenidoğan yoğun bakım ünitesinde yüksek akışlı nazal kanül (HFNC), nazal sürekli pozitif hava yolu basıncı (NCPAP) veya nazal aralıklı pozitif basınçlı ventilasyon (NIPPV) ile tedavi edilen ASYE'lu yenidoğanlarda prospektif bir çalışma yürütüldü. Yöntemin başarısızlığı, klinik ve laboratuvar bulgularına göre 6 saat içinde başka bir NIV yöntemine geçmek olarak tanımlandı. Gruplar klinik ve laboratuvar bulguları, hastanede kalış süresi, sonuçlar, başarı oranları ve komplikasyonlar açısından karşılaştırıldı.

Bulgular: Çalışmaya medyan gebelik yaşı 38 hafta ve doğum ağırlığı 2991±673 g olan toplam 106 yenidoğan dahil edildi. Kabuldeki Downes skorları NCPAP grubunda diğerlerinden anlamlı olarak daha yüksekti. HFNC grubunda kan pH ve CO2 seviyelerinde daha iyi sonuçlar saptanmasına rağmen daha yüksek oranda tedavi başarısızlığı görüldü. NCPAP en yüksek başarı oranıyla (%86.8) ilişkiliydi, bunu NIPPV (%78.7) ve HFNC (%52.4) izledi. NCPAP ve NIPPV ile başarılı bir şekilde tedavi edilen hastaların hastanede kalış süreleri daha kısaydı. Lojistik regresyon analizine göre NIPPV HFNC ile karşılaştırıldığında başarısızlık riskini anlamlı şekilde azalttı.

Sonuç: NIPPV ve NCPAP, daha kısa hastane yatışıyla neonatal ASYE'nu yönetmede HFNC'den daha etkiliydi. Neonatal ASYE'nda, HFNC bazal solunum parametrelerini stabilize etmede etkili olabilir.

Anahtar kelimeler: Yüksek akışlı nazal kanül, alt solunum yolu enfeksiyonu, nazal CPAP, nazal IPPV, yenidoğan, non-invaziv ventilasyon.

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INTRODUCTION

Acute respiratory tract infections are among the most common medical emergencies in early infancy and can require hospitalization, especially for neonates[1]. Moreover, acute lower respiratory tract infections (LRTI) are among the leading causes of morbidity and mortality among neonates in developing countries. Antibiotherapy and respiratory support are often needed for treatment[2,3]. The management of LRTIs in neonatal intensive care units is mostly based on a clinical evaluation of the patient and the clinician's judgment and previous experience.

Newer modalities of non-invasive ventilation (NIV) strategies that have been introduced into neonatal practice in the last two decades include heated and humidified high-flow cannula (HFNC), non-invasive positive pressure ventilation (NIPPV) and nasal continuous positive airway pressure (nCPAP)[4]. Various methods of respiratory support are currently used for LRTI, including standard oxygen therapy, HFNC, NIPPV, NCPAP, and invasive mechanical ventilation (IMV). However, NIV methods have become the preferred treatment for respiratory problems because they prevent some complications associated with intubation and mechanical ventilation, also reducing the length of hospital stay[5]. In infants with severe bronchiolitis, NCPAP and HFNC are the more frequently used NIV methods and can improve the physiological and clinical results associated with respiratory distress[6]. The use of HFNC has been reported as a first-line treatment for newborns with bronchiolitis or viral respiratory tract infections requiring respiratory support[3]. After recognizing its efficacy in acute bronchiolitis in children, HFNC has also been applied in diseases such as pneumonia and asthma[7,8].

Hypoxemia is an important risk factor for mortality in children diagnosed with acute LRTI. Effective management of hypoxemia and LRTI is important for survival [9]. If respiratory failure does not respond to NIV in these patients, they are switched to IMV[3]. The need for IMV has been shown to be reduced by NIV [10]. Therefore, the aim is to reduce the need for mechanical ventilation and ventilator-associated complications by providing adequate NIV support to patients with respiratory distress.

The continuous positive pressure provided by NCPAP is important for alveolar healing [11]. This pressure can be monitored and regulated during NCPAP. NIPPV also delivers an inspiratory peak pressure of the specified rate and pressure over PEEP [12]. Although HFNC also creates positive airway pressure, it cannot be monitored and regulated [13]. It can be concluded that HFNC may not adequately meet the pressure needs of neonates who develop respiratory distress due to LRTI, and when pressure requirement is anticipated, it can be better met with NCPAP and NIPPV.

The present study compared the effectiveness of different NIV methods by comparing the complications, response to treatment, and length of hospital stay of neonates with LRTI who received NIV.

MATERIALS AND METHODS

Sample

The study included infants who were admitted to the 3-level neonatal intensive care unit of Ankara Pediatrics Hematology Oncology Training and Research Hospital, Ankara Bilkent City Hospital for LRTI, needed respiratory support, and received NIV between 2018 and 2022. The choice between nCPAP, HFNC and NIPPV was made by attending physician based on clinical judgment considering factors such as the severity of respiratory distress, laboratory findings and the overall stability of the infant. After the patients were admitted to NIV, their respiratory parameters, laboratory findings and clinical status were closely monitored by the clinician, and necessary changes and adjustments were made at the clinician's discretion.

Indications for hospitalization

1) Respiratory distress (defined as a respiratory rate >60/minute and presence of intercostal/subcostal retractions, wheezing, coughing, and apnea) with hypoxia (defined as pulse oximeter measurement of oxygen saturation [SpO_2] <90% on room air)

2) Impaired circulation (defined as low blood pressure, tachycardia, and prolonged capillary refill time)

3) Respiratory distress accompanied by impaired feeding. The presence of one or more of these indications was sufficient for admission. The patients' radiological data (chest X-ray) and laboratory results (hemogram, peripheral blood smear, blood gas analysis, and C-reactive protein [CRP]) were analyzed. Nasopharyngeal swab samples were obtained within the first hour of admission for

multiplex reverse transcription-polymerase chain reaction (*RT-PCR*) analysis for human rhinovirus, respiratory syncytial virus, human parainfluenza virus, human metapneumovirus, human immunodeficiency virus, human bocavirus, adenovirus, coronavirus, and enterovirus. Blood samples for culture were obtained prior to initiating of antibiotic therapy.

In patients with respiratory distress, the need for NIV was determined based on clinical findings, signs of tissue hypoxia, vital signs, SpO_2, arterial blood gases, blood lactate level, and the Silverman-Anderson and Downes scores. The Silverman-Anderson Score is based on xiphoidal-intercostal retraction, chest movements, nasal flaring, and grunting on expiration, with a score >7 evaluated as respiratory failure[14]. The Downes score is based on respiratory rate, cyanosis, retraction, grunting, and air entry, with a score >6 evaluated as respiratory failure[15]. If the patient's SpO_2 remained below the target SpO_2, hypercapnia or clinical symptoms did not improve, pressure support or oxygen support was increased. Treatment failure was defined as the need for intubation or switching the method within 6 hours of starting NIV. Patients' NIV, supplemental oxygen support, and length of hospital stay were compared.

Neonates with other known diseases, genetic disorders (n=3), congenital anomalies (n=2), or congenital heart (n=2) or metabolic disorders (n=1) and those intubated within the first 6 hours of treatment (n=12) were excluded from the study.

NIV methods

NCPAP was provided via short binasal prongs (INCA, Ackrad Labs/Cooper Surgical, Trumbull, Connecticut, USA and Care Fusion, Yorba Linda, USA) using a neonatal ventilator (SLE; Specialized Laboratory Equipment, South Croydon, England). Positive end-expiratory pressure (PEEP) was adjusted to 5-6 cmH_2O. NCPAP was continued until PEEP was 5 cmH_2O, the fraction of inspired oxygen (FiO_2) was below 30%, and clinical signs of respiratory distress had resolved.

NIPPV was administered via short binasal prongs (INCA) using a neonatal ventilator (SLE) in non-synchronous mode. PEEP was set to 5-6 cmH_2O, peak inspiratory pressure (PIP) to 15-20 cmH_2O, inspiration time to less than 0.35-0.5 s, and respiratory rate to 30-40/min (max PEEP: 7 cmH_2O, max PIP: 25 cmH_2O, max respiratory rate: 60/min). NIPPV was continued until PIP was 10-15 cmH_2O or lower, PEEP was 5 cmH_2O or lower, respiratory rate was 15/min or lower, FiO_2 was below 30%, and signs of respiratory distress had resolved.

HFNC was provided using an Airvo™ 2 with Optiflow nasal cannula (Fisher & Paykel Healthcare, New Zealand). Flow rate was set to 2 L/kg/min and increased up to a maximum of 8 L/min.

NIV failure criteria

The decision to switch NIV method within 6 hours of initiation (NIV failure) was made in the presence of at least one of the following criteria: hypoxemia (FiO_2 >50% to achieve target SpO_2), respiratory acidosis (pH <7.2 and partial pressure of carbon dioxide [pCO_2] >65 mmHg), and recurrent apnea[16].

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Clinical Research Ethics Committee of Ankara Pediatrics Hematology Oncology Training and Research Hospital (2018-103/25.06.2018). Informed consent was obtained from the parents.

Statistical analysis

All statistical analyses were performed using Jamovi (Version 2.3.28) and JASP (Version 0.18.3), with a two-sided significance level set at 0.05. Continuous variables were initially evaluated for normality using Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests. Normally distributed continuous variables (e.g., birth weight, arterial pH) were summarized as mean ± standard deviation and compared across groups using the Independent Samples t-test (for two-group comparisons) or One-Way ANOVA (for comparisons among three groups: HFNC, NIPPV, and NCPAP). Post-hoc comparisons for parametric tests were conducted using the Tukey or Games-Howell test, as appropriate. For non-normally distributed continuous variables (e.g., Downes scores, duration of hospital stay), data were presented as median [minimum–maximum], and comparisons were made using the Mann-Whitney U test (two groups) or Kruskal-Wallis H test (three groups), followed by the Dwass-Steel-Critchlow-Fligner test for multiple comparisons. Categorical variables (e.g., success of NIV method, presence of a specific pathogen) were expressed as counts and percentages and compared between groups using the Chi-square test or Fisher's exact test, when cell counts were low.

To identify factors associated with the success of the non-invasive ventilation (NIV) method, univariable and multivariable logistic regression analyses were conducted. Initially, each candidate predictor (such as type of NIV [HFNC, NIPPV, NCPAP], Downes score, presence of specific viral pathogens, and chest X-ray findings) was assessed in separate univariable models. Variables with $p<0.10$ in the univariable analysis or those deemed clinically relevant based on prior evidence and neonatal respiratory pathology (e.g., Downes score) were subsequently included in the multivariable logistic regression model. This approach ensured a parsimonious model while retaining factors with potential clinical or statistical importance. The multivariable model provided adjusted odds ratios (OR) with 95% confidence intervals (CIs) and p-values, thus accounting for the combined effect of all included variables. The final model evaluated the independent associations of NIV methods and clinical/laboratory parameters with treatment success.

RESULTS

The study included 106 patients with a median gestational age at birth of 38 weeks and mean birth weight of 2991±673 g. SpO_2 levels at admission were significantly higher in the infants who received HFNC than in those who received NIPPV or NCPAP ($p=0.04$ and $p=0.013$, respectively). Heart rate at admission was higher in the NCPAP group than in the NIPPV group ($p=0.038$), while Downes scores was higher in the NCPAP group than in the HFNC and NIPPV groups ($p<0.001$ for both) (Table 1).

Table 1. Patients' demographic and clinical characteristics.

Variable	Overall (n=106)	HFNC (n=21)	NIPPV (n=47)	NCPAP (n=38)	p value
Gestational age (weeks)§	38 [28.3- 42]	38 [36 - 41]	38 [28.3- 42]	37.2 [30- 40.3]	0.10*
Birth weight (g)†	2991 ± 673	3260 ± 419	3053 ± 647	2766 ± 757	0.008**
Delivery Type (CS)‡					
					0.13***
	71 (67)	12 (57.1)	29 (61.7)	30 (78.9)	
Gender (Male)‡					
					0.35***
	63 (59.4)	12 (57.1)	25 (53.2)	26 (68.4)	
Age of mother†	28.7 ± 6.6	27.4 ± 6.5	28.1 ± 5.6	30.2 ± 7.7	0.27**
Postnatal age at admission (days)§	23 [3 - 78]	23 [7 - 28]	23 [8 - 78]	24 [3 - 76]	0.055*
Body weight at admission (g)†	3605 ± 686	3597 ± 556	3630 ± 715	3578 ± 730	0.94**
Oxygen saturation (mmHg)†	90 ± 6	94 ± 5	90 ± 6	89 ± 6	0.005**
Heart rate (/min)§	161[84 - 200]	158 [134- 185]	157 [112 - 200]	169 [84 - 196]	0.024*
Respiratory rate (/min)†	62 ± 12	59 ± 11	61 ± 11	66 ± 13	0.092**
Silverman-Anderson Score§	4.5 [2 - 33]	4 [3 - 33]	4 [2 - 7]	5 [2 - 8]	0.13*
Downes Score§	5 [2 - 9]	3 [2 - 7]	5 [2 - 8]	6 [3 - 9]	<0.001*

NIV: Non-invasive ventilation, HFNC: High-flow nasal cannula, NIPPV: Nasal intermittent positive pressure ventilation, NCPAP: Nasal continuous positive airway pressure.; ‡: n (%), †: Mean ± standard deviation, §: Median [range]; *Kruskal-Wallis H test.; **One-way ANOVA.; ***Pearson chi-square test.

Both arterial pH and pCO_2 differed significantly among the groups ($p<0.001$). Admitting blood pH values were significantly higher in the HFNC group compared to the NIPPV and NCPAP groups ($p=0.053$ and $p<0.001$, respectively), while blood pCO_2 was significantly lower in the HFNC group compared to the NIPPV and NCPAP groups ($p=0.002$ and $p<0.001$, respectively). CRP levels and immature/total neutrophil ratios also showed significant variations. Particularly, CRP levels were lower in the HFNC group compared to the other groups ($p=0.001$) (Table 2).

Table 1. Results of the infants' initial laboratory analyses.

Variable	Overall (n=106)	HFNC (n=21)	NIPPV (n=47)	NCPAP(n=38)	p value
Arterial pH †	7.3 ± 0.1	7.4 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	**<0.001****
pCO_2 (mmHg)†	48.3 ± 9.8	40.6 ± 7	48.9 ± 10.6	52.2 ± 7.3	**<0.001****
Blood lactate (mmol/L)§	2.6 [0.2- 14.0]	2.3 [1.1- 9.9]	2.7 [0.2- 9.2]	2.8 [1.1- 14.0]	0.11*
Leukocyte count (mm^3)§	9600 [2600- 28500]	9100 [6400- 28500]	9600 [2870- 22100]	9600 [2600- 22100]	0.47*
C-reactive protein (mg/dl)§	1.7 [0- 106]	0.5 [0- 15.5]	1.7 [0- 106]	5.2 [0.5- 59.1]	**0.001***
Immature/total neutrophil ratio§	0.1 [0- 0.8]	0.1 [0.1- 0.3]	0.2 [0- 0.8]	0.1 [0- 0.2]	**0.013***
Positive blood culture‡	3 (2.8)	1 (4.8)	2 (4.3)	0 (0.0)	0.42***
Positive respiratory virus panel‡	79 (74.5)	14 (66.7)	37 (78.7)	28 (73.7)	0.56***
Respiratory virus panel results, if available‡					
RSV	65 (82.3)	13 (92.9)	30 (81.1)	22 (78.6)	0.10***
Rhinovirus	5 (6.3)	0 (0)	5 (13.5)	0 (0)	
Coronavirus	3 (3.8)	1 (7.1)	0 (0)	2 (7.1)	
Bordetella pertussis	1 (1.3)	0 (0)	1 (2.7)	0 (0)	
Haemophilus influenza	2 (2.5)	0 (0)	0 (0)	2 (7.1)	
Streptococcus pneumonia	1 (1.3)	0 (0)	0 (0)	1 (3.6)	
Influenza	2 (2.5)	0 (0)	1 (2.7)	1 (3.6)	
Chest X-ray‡					
Over-aeration	8 (7.5)	2 (9.5)	4 (8.5)	2 (5.3)	0.55***
Reticulogranular pattern	43 (40.6)	7 (33.3)	17 (36.2)	19 (50)	
Consolidated area	43 (40.6)	8 (38.1)	23 (48.9)	12 (31.6)	
Normal	7 (6.6)	3 (14.3)	2 (4.3)	2 (5.3)	
Atelectasis	4 (3.8)	1 (4.8)	1 (2.1)	2 (5.3)	
Infiltration	1 (0.9)	0 (0)	0 (0)	1 (2.6)	

HFNC: High-flow nasal cannula, NIPPV: Nasal intermittent positive pressure ventilation, NCPAP: Nasal continuous positive airway pressure.; ‡: n (%), †: Mean ± standard deviation, §: Median [range]
*Kruskal-Wallis H test.; **One-way ANOVA test.; ***Pearson chi-square or Fisher-Freeman-Halton test.

In this study, we classified the patients as successful (n=81) and unsuccessful (n=25) NIV support. The success rate was significantly higher in the NIPPV and NCPAP groups compared to the HFNC group (p=0.011). The NCPAP group had a significantly shorter length of hospital stay compared to NIPPV group (p=0.032) and lower duration of antibiotic therapy in the NCPAP group compared to HFNC and NIPPV groups (p<0.001 for both). Comparison of the antibiotic therapy given showed that clarithromycin was used more frequently in the HFNC and NCPAP groups than in the NIPPV group (p=0.029). The usage of other antibiotics and antibiotic combinations was similar across the groups. There was no difference in complication rates between the NIV methods (p>0.05) (Table 3).

Table 2. The clinical findings of the infants according to NIV method.

Variable	Overall (n=106)	HFNC (n=21)	NIPPV (n=47)	NCPAP (n=38)	P value
Success of NIV method‡					
Successful	81 (76.4)	11 (52.4) [a]	37 (78.7) [b]	33 (86.8) [b]	0.011***
Failed	25 (23.6)	10 (47.6) [a]	10 (21.3) [b]	5 (13.2) [b]	
HFNC Duration (days)§	2 [1- 6]	2 [1 - 6]	-	-	-
NIPPV Duration (days)§	3 [0.2- 8]	5 [5 - 5]	3 [0.5- 8]	3 [0.2- 6]	0.5*
Total NIV Duration (days)§	4 [1- 9]	3.5 [2- 8]	4 [1 - 8]	3 [2 - 9]	0.85*
Maximum FiO_2 (%)§	30 [21 - 60]	30 [25 - 40]	30 [21- 60]	35 [25 - 50]	0.004*
Switched to IMV‡	16 (15.1)	1 (4.8)	10 (21.3)	5 (13.2)	0.22***
Duration of IMV (days)§	4.5 [1- 13]	3 [3 - 3]	5.5 [1- 13]	4 [1- 7]	0.62*
Developed complication‡	15 (14.2)	2 (9.5)	9 (19.1)	4 (10.5)	0.49***
Complications‡					
Nasal trauma	11 (73.3)	2 (100)	8 (88.9)	1 (25)	0.12***
Atelectasis	3 (20.0)	0 (0)	1 (11.1)	2 (50)	
Nosocomial infection	1 (6.7)	0 (0)	0 (0)	1 (25)	
Received inhaled bronchodilator therapy‡	59 (55.7)	15 (71.4)	27 (57.4)	17 (44.7)	0.13***
Received antibiotic therapy‡	97 (91.5)	21 (100) [a]	45 (95.7) [a]	31 (81.6) [b]	0.027***
Antibiotic therapies‡					
Ampicillin + Gentamicin	19 (19.6)	4 (19) [a]	7 (15.6) [a]	8 (25.8) [a]	0.029***
Ampicillin + Cefotaxime	14 (14.4)	1 (4.8) [a]	9 (20) [a]	4 (12.9) [a]	
Clarithromycin	10 (10.3)	5 (23.8) [a]	1 (2.2) [b]	4 (12.9) [a,b]	
Ampicillin + Gentamicin + Clarithromycin	30 (30.9)	9 (42.9) [a]	11 (24.4) [a]	10 (32.3) [a]	
Teicoplanin + Cefotaxime	5 (5.2)	0 (0) [a]	4 (8.9) [a]	1 (3.2) [a]	
Ampicillin + Cefotaxime + Clarithromycin	9 (9.3)	0 (0) [a]	7 (15.6) [a]	2 (6.5) [a]	
Ampicillin + Cefotaxime + Oseltamivir	4 (4.1)	2 (9.5) [a]	2 (4.4) [a]	0 (0) [a]	
Ampicillin + Gentamicin + Oseltamivir	4 (4.1)	0 (0) [a]	4 (8.9) [a]	0 (0) [a]	
Oseltamivir	1 (1)	0 (0) [a]	0 (0) [a]	1 (3.2) [a]	
Vancomycin + Meropenem	1 (1)	0 (0) [a]	0 (0) [a]	1 (3.2) [a]	
Duration of antibiotics (days)§	10 [2 - 25]	10 [7 - 20]	10 [5 - 25]	7 [2- 14]	<0.001*
Duration of additional O_2 support (days)§	3 [0.5- 9]	3 [1 - 7]	3 [1 - 8]	3 [0.5- 9]	0.13*
Duration of hospital stay (days)§	10 [3 - 2]	10 [7 - 20]	10 [7 - 27]	9 [3 - 17]	0.028*

NIV: Non-invasive ventilation, HFNC: High-flow nasal cannula, NIPPV: Nasal intermittent positive pressure ventilation, NCPAP: Nasal continuous positive airway pressure.; ‡: n (%), †: Mean ± Standard Deviation, §: Median [Min.-Max.]
*Kruskal-Wallis H test.; **One-way ANOVA.; ***Pearson chi-square or Fisher-Freeman-Halton test.

In this study, logistic regression analysis was applied to analyze factors affecting the success of NIV method. In the univariable analyses, NIPPV and NCPAP had significantly higher success rates. NIPPV had the most significant success rate, with an odds ratio (OR) of 0.30 (confidence interval [CI] 0.10-0.89, p=0.031). NCPAP application also showed a strong effect, increasing the likelihood of success with an OR of 0.17 (CI 0.04-0.57, p=0.006). The results of the multivariable analysis indicated that the adjusted OR for NIPPV group was 0.25 (CI 0.07-0.81, p=0.022), and the adjusted OR was 0.15 (CI 0.04-0.54, p=0.005) for NCPAP group.

The results of the multivariable analysis indicated that the adjusted OR for the NIPPV group was 0.14 (CI 0.03-0.51, p=0.004), and the adjusted OR was 0.04

(CI 0.01-0.21, p<0.001) for the NCPAP group. The Downes Score showed significant differences for the groups with an adjusted OR of 1.70 (CI 1.21-2.49, p=0.004). The positivity in the respiratory virus panel and the findings in the PA chest X-ray (aeration differences, RG appearance, and consolidated group) did not have a significant effect in the multivariable model (p>0.05 for each) (Table 4).

Table 4. Predictors of NIV success (univariable and multivariable analysis).

Dependent: NIV success	Univariate OR (95% CI), p value	Multivariate OR (95% CI), p value
NIV methods		
HFNC (reference)	-	-
NIPPV	0.30 (0.10-0.89) p=0.031	0.14 (0.03-0.51) p=0.004
NCPAP	0.17 (0.04-0.57) p=0.006	0.04 (0.01-0.21) p<0.001
Downes Score	1.22 (0.95-1.60) p=0.126	1.70 (1.21-2.49) p=0.004
Positive Respiratory Virus Panel	2.08 (0.70-7.72) p=0.221	2.88 (0.83-12.40) p=0.11
Chest X-ray		
Aeration problem (reference)	-	-
Reticulogranular appearance	0.44 (0.09-2.38) p=0.302	0.39 (0.07-2.62) p=0.3
Consolidation	0.76 (0.17-4.04) p=0.730	0.62 (0.11-4.16) p=0.6

NIV: Non-invasive ventilation, HFNC: High-flow nasal cannula, NIPPV: Nasal intermittent positive pressure ventilation, NCPAP: Nasal continuous positive airway pressure, OR: Odds ratio, CI: Confidence interval

DISCUSSION

In this study, we compared the effectiveness of three non-invasive respiratory support methods–HFNC, NCPAP, and NIPPV–in neonates with LRTI. Switching to another respiratory support method within 6 hours of starting NIV because clinical and/or laboratory findings worsened or failed to improve was considered failure in these patients. Of the applied NIV methods, failure rates were lower in NCPAP and NIPPV when compared with HFNC. In addition, length of hospital stay was found to be longer in neonates who received HFNC compared to other methods.

Neonatal LRTI can lead to the need for respiratory support, and different clinics use different methods of NIV that are not supported by high-level evidence. Personal preferences, routine practices, and the resources available in the clinic are among the main factors that determine which respiratory support method is used. However, understanding which method will be effective and should be preferred is based more on observational and cohort studies and improved physiological data [17]. HFNC has increased in popularity among clinicians because it is less invasive than NCPAP and easy to apply[18]. The use of HFNC in respiratory diseases has increased in recent years and is no longer limited to infants with bronchiolitis [19]. Chisti et al. compared NCPAP and standard oxygen support in patients diagnosed with pneumonia before the age of 5 and reported that NCPAP reduced mortality, but they observed no difference between NCPAP and HFNC [20]. In a study of 67 pediatric clinics from Germany, 70% of clinics preferred the use of HFNC as supportive therapy after pneumonia and extubation due to lack of cooperation with NCPAP. In addition, 12 of the 67 clinics used HFNC for neonates. Many clinics reported that NCPAP is not well tolerated by patients, and HFNC is preferred as an alternative when continuous PEEP is needed [21]. In our study, HFNC, NIPPV, and NCPAP were applied to newborns with LRTI, and the failure rate was found to be higher with HFNC. Therefore, although HFNC is considered as a first-line treatment for newborns with LRTI, it may not appear to be a viable alternative to NCPAP and NIPPV.

In a review evaluating the use of HFNC in neonates, children, and adults, HFNC was not found to be equal or superior to other NIV methods [11]. A review of eight studies stated that there was not enough evidence to formulate evidence-based guidelines on

the use of HFNC for respiratory failure in term infants [22]. In a retrospective study evaluating 113 infants that received HFNC for viral bronchiolitis, patients who did not respond to treatment were found to be more hypercarbic [23]. In a pediatric intensive care unit where patients with asthma, pneumonia, and congenital heart disease received HFNC (27%) over a period of 2 years, the failure rate was found to be 5.8% and HFNC treatment was reported to be well tolerated [8]. In another study encompassing a wide age range, HFNC was found to be effective and reduce intubation rates in pediatric intensive care patients with bronchiolitis, pneumonia, asthma, and croup[24]. In a multicenter study comparing NCPAP and HFNC in 754 neonates with respiratory distress (mean gestational age: 36.9, mean birth weight: 2909 g), treatment failure was found to be higher in HFNC[25]. Yoder et al. compared NCPAP and HFNC in 432 infants born a gestational age of 28-42 weeks and observed no difference in terms of early failure or intubation requirement and found that the duration of HFNC support was longer, similar to our study[26]. Although in our study the neonates with LRTI who received HFNC had a better laboratory and clinical status (lower Downes score), the failure rate with HFNC was higher and there was no difference in IMV requirement between patients who received HFNC, NCPAP, and NIPPV.

Preferring NIV methods for respiratory support is recommended for neonates. However, continuous or intermittent positive pressure delivered to the airways can cause some undesirable problems, especially when the infant is not in sync with the device. PEEP, which in HFNC cannot be measured and is variable, can cause excessive distension in the lungs and nasopharyngeal area. Although HFNC is considered a less invasive method, a study emphasizing its potential to cause serious adverse effects reported a 17.9% rate of pneumothorax[21]. In our study, no air leak was observed with any of the NIV methods. This may be related to the close and continuous monitoring of the patients, the proper and timely care, intermittent repositioning, careful implementation of the specified flow rates and pressures, and the use of nasal prongs appropriate for the patient and device. Janota et al. explored the impacts of oximeter averaging times on automated FiO2 control, underscoring the complexity of managing respiratory support in neonates and the delicate balance required to optimize outcomes. This study emphasizes the nuanced approach needed in respiratory management to prevent over-oxygenation and related complications[27].

Nasal trauma is among the most common complications that can occur in NIV, depending on the nasal prong or mask used. In addition, unheated and unhumidified high-flow gases increase the risk of damage by causing desiccation and bleeding in the nasal mucosa. The heated, humidified airflow in HFNC prevents significant irritation of the nasal mucosa[28]. However, the literature includes studies showing that HFNC reduces, increases, or causes a similar rate of nasal trauma compared to NCPAP[21,26]. In our study, nasal prongs were used as the interface in all three groups, and no difference was found between the groups in terms of complications. We attribute the low rate of adverse effects in our study to the regular and careful care provided to avoid nasal trauma. These findings are corroborated by Kumar et al., who examined the periodic rotation versus continuous application of nasal interfaces in preterm neonates. They emphasize the need for tailored respiratory support strategies to minimize complications and improve outcomes, which supports our study[29].

NIPPV is an NIV mode that works by providing inspiratory pressure ranging from 10 to 20 cmH_2O over PEEP for primary respiratory support. NIPPV has been shown to reduce respiratory effort in infants with respiratory distress syndrome (RDS) compared to NCPAP[30]. When NIPPV, NCPAP, and HFNC were evaluated in RDS, NIPPV was superior to NCPAP, while HFNC was also found to be beneficial[31]. In our study, NIPPV and NCPAP showed similar effectiveness. The different results obtained regarding their efficacy may be related to differences in the physiopathology of RDS and LRTI.

The Silverman-Anderson score can be used to determine the severity of respiratory failure, especially in premature infants, and the Downes score can be used in all neonates regardless of gestational age at birth[14,15]. In a study by Buch et al., the Downes score was found to be effective in predicting bubble NCPAP failure in preterm infants with RDS[32]. In this study, we evaluated the role of these scores in predicting the severity of respiratory failure in neonates with LRTI. In logistic regression analysis, the Downes score was found to be effective in predicting the success of NIV. Based on this result, it can be recommended that the Downes score be used to determine the need for respiratory support in neonates with respiratory failure.

To the best of our knowledge, there are no studies in the literature comparing HFNC, NCPAP, and NIPPV results in neonates with LRTI. During the study, patients were closely and continuously monitored in terms of NIV efficacy and complications. Therefore, the neonates received the needed treatment in a timely and effective manner.

The prospective design of our study is its greatest strength. However, one of the primary limitations is the relatively small sample size. With 106 patients distributed across three intervention groups (HFNC, NCPAP, and NIPPV), the statistical power to detect small but clinically significant differences between the groups is limited. This size constraint may particularly impact the robustness of subgroup analyses where patient numbers were further reduced, possibly affecting the precision of the estimated effects.

In conclusion, our study offers valuable insights into the comparative effectiveness of HFNC, NCPAP, and NIPPV in managing neonates with LRTI, although the abovementioned limitations should be considered when interpreting the results. Prior studies have identified non-invasive ventilation (NIV) as a crucial strategy in neonatal care, particularly for managing respiratory issues with minimal invasiveness. However, comparative data on HFNC, NCPAP, and NIPPV's efficacy and safety in neonatal pneumonia were limited. Our study fills this gap by meticulously analyzing treatment outcomes associated with each method. We demonstrate that NCPAP, followed by NIPPV, significantly outperforms HFNC in treatment success rates, and hospitalization duration. These findings provide concrete evidence supporting the preferential use of NIPPV and NCPAP in severe neonatal pneumonia, potentially guiding future clinical protocols and training initiatives to optimize neonatal respiratory care. Randomized controlled trials with a multicenter design and larger sample sizes will be crucial to confirm these findings and explore the long-term outcomes associated with these NIV strategies.

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Ethical Approval: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Clinical Research Ethics Committee of Ankara Pediatrics Hematology Oncology Training and Research Hospital (2018-103/25.06.2018). Informed consent was obtained from the parents.
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