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Salbutamol Plus Mask Oxygen Versus HFNC in Bronchiolitis

Bronşiolitte Salbutamol Plus Maske Oksijen ve HFNC Karşılaştırması

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Abstract

Introduction: As the benefit of many pharmacologic treatments for bronchiolitis is a source of debate, investigations of more effective, easy-to-apply treatment modalities of acute bronchiolitis remain up-to-date.

Methods: In this study, nebulised salbutamol plus standard oxygen (S) and HFNC (HF) therapies were administered to children younger than two years of age, with a respiratory clinical score (RCS) ≥4 points, who presented with a first episode of acute bronchiolitis.

Results: The mean age of 72 patients was 7.8±0.4, and 59.7% were younger than six months. The mean RCS of the patients at admission was 8.42±2.026 points. A significant decrease was observed in the mean RCS scores evaluated at 1-2-4-8 hours, from the first hour ($p<0.05$). The mean length of hospital stay and duration of oxygen therapy were 70±64.6 (4-288) and 67.7±62.2 (4-264) hours. Within the first few days after discharge, 50% of the patients returned to the pediatric emergency department (PED). The mean RCS showed a difference in favour of the HF group from the second hour of treatment ($p=0.002$). Expected improvement was not observed in 17.1% of the patients in the S group only, thus HF should be added. Patients in the HF group and patients in whom HF was added to S had higher hospitalisation rates ($p=0.017$), longer hospital stays ($p=0.002$), and longer duration of oxygen therapy ($p=0.001$). Re-admission to PED after discharge was observed in 64.2% of the cases in the S group only ($p<0.001$).

Conclusion: In this study, it may be said that HFNC treatment provides earlier and faster clinical improvement in children with bronchiolitis and reduces re-admissions related to the same disease.

Keywords: Acute bronchiolitis, salbutamol, high flow nasal oxygen therapy

Öz

Giriş: Bronşiolit için birçok farmakolojik tedavinin faydası tartışma konusu olduğundan, akut bronşiolit için uygulanması kolay daha etkili tedavi yöntemlerinin araştırılması konusu güncelliğini korumaktadır.

Yöntemler: Bu çalışmada; iki yaşından küçük, solunum klinik skoru (RKS) ≥4 puan olan ve ilk akut bronşiolit atağıyla gelen çocuklara nebulize salbutamol + artı standart oksijen(S) ve yüksek akışlı nazal kanül oksijen tedavisi (HF) tedavileri uygulandı.

Bulgular: Yetmiş iki hastanın ortalama yaşı 7,8±0,4 idi ve %59,7'si altı aydan küçüktü. Hastaların kabul anındaki ortalama RKS'si 8,42±2,026 puandı. İlk saatten itibaren 1-2-4-8 saatte değerlendirilen ortalama RKS skorlarında anlamlı bir düşüş gözlendi ($p<0,05$). Hastanede kalış süresi ve oksijen tedavisinin süresi ortalamaları sırasıyla 70±64,6 (4-288) ve 67,7±62,2 (4-264) saatti. Taburcu olduktan sonraki ilk birkaç gün içinde hastaların %50'si tekrar çocuk acil servisine (PED) başvurdu. Ortalama RKS, tedavinin ikinci saatinden itibaren HF grubunun lehine farklılık gösterdi ($p=0,002$). Sadece S grubunda hastaların %17,1'inde beklenen iyileşme görülmedi ve HF eklenmesi gerekti. HF grubundaki hastalar ve S'ye HF eklenen hastalarda daha yüksek hastane yatış oranları ($p=0,017$), daha uzun hastanede kalış süreleri ($p=0,002$) ve daha uzun oksijen tedavisi süreleri ($p=0,001$) vardı. Taburcu olduktan sonra PED'ye tekrar başvuru sadece S grubunda %64,2 oranında görüldü ($p<0,001$).

Sonuç: Bu çalışmada; HFNC tedavisinin bronşiolitli çocuklarda daha erken ve daha hızlı klinik iyileşme sağladığı ve aynı hastalığa bağlı tekrar yatışları azalttığı söylenebilir.

Anahtar Kelimeler: Akut bronşiolit, salbutamol, yüksek akımlı nazal oksijen tedavisi

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Introduction

As the benefit of many pharmacologic treatments for bronchiolitis is a source of debate, supportive care, including supplemental oxygen for hypoxemia, is currently the mainstay of treatment for bronchiolitis.[1-4] Recently, various clinical studies have reported that the high-flow nasal cannula oxygen therapy system (HFNC) may be a safe treatment option that can improve SpO_2, respiratory rate, heart rate, and blood gas parameters in paediatric patients with acute lower respiratory tract infections.[5-8] However, as in many parts of the world, physicians continue to manage patients in our country with their individual experiences and decisions.[9,10]

Objective

The aim of this study is to perform a non-blind, open label, quasi-randomised, prospective crossover trial in infants under 24 months with a first clinically diagnosed bronchiolitis, comparing nebulised salbutamol plus standard mask oxygen therapy to HFNC therapy in a paediatric emergency setting in our center. The primary outcome is treatment success of salbutamol plus standard mask oxygen or HFNC therapy. Treatment success is defined as a decrease of at least two points in respiratory clinical score (RCS) scores or a downward change in the clinical severity category of the patients. Secondary outcome measures comprise (a) the rate of hospitalisation; (b) length of stay in hospital; (c) the rate of transfer of children to the pediatric intensive care unit; (d) length of oxygen therapy; (e) measurement of patients' comfort scores; (f) measurement of adverse side effects.

Materials and Methods

We included infants with the diagnosis of acute bronchiolitis that is defined as a viral respiratory infection with nasal discharge and wheezy cough, and in the presence of fine inspiratory crackles, or high-pitched expiratory wheeze on admission to the pediatric emergency room. Inclusion criteria were; infants aged ≤24 months with their first acute bronchiolitis attack, RCS ≥4 points, and/or having SpO_2<94% on room air, and/or having respiratory acidosis in their blood gases. Infants with previous episodes of wheezing, any chest or upper airway deformity and/or trauma limiting respiratory function, chronic (cardiac, respiratory, immunological, neurological, or metabolic) disease under treatment, and urgent need for advanced respiratory support on admission were excluded.

In our prospective clinical intervention study, patients were selected according to the pre-specified criteria mentioned above, and every 4th patient was randomized to receive HFNC oxygen therapy considering the limits of the study budget. During the assignment of patients to treatment groups, ranking numbers were used to determine that every fourth patient would be in the HFNC group, and the total number of patients who started with and those who added HFNC treatment was restricted to the available sets. The allocation of patient to the treatment groups using method that were not truly random but intended to produce similar groups This quasi-randomization was used because true randomization was not feasible. Emergency department staff were not blinded in terms of the implementation of treatment, clinical evaluation, and scoring. Our study was planned and conducted as a pediatric resident thesis. The assistant physician and the responsible faculty member, who collected and evaluated the study data, were not involved in the treatment process and clinical evaluation of study patients. Ethical approval was obtained from the Local Clinical Researches Ethics Committee of Akdeniz University (15.11.2017-674), and the trial was overseen by a steering committee, consisting of senior pediatrics faculty members, for the ethical and rigorous conduct of the trial. Governance approval from the university hospital has been obtained. There was no registration in another clinical study system. Informed written consent was obtained from a parent of each child.

All patients were clinically evaluated for study inclusion by pediatric emergency department (PED) physicians using standard history and physical examination. The RCS system is a reliable scoring method that can be calculated quickly and easily, with 0-4 points indicating mild severity,[5-8] points indicating moderate severity, and 9-12 points indicating severe respiratory distress clinical category.[11-13] The RCS takes into account the 4 parameters, namely, respiratory rate, retractions, dyspnea, and wheezing. Each parameter is scored in four steps, with scores ranging from 0 to 3 points, as shown in Figure 1. Pretrained PED physicians assessed the RCS score of patients included in the study just before the allocation, and at the 1st, 2nd, 4th, and 8th hour of treatment.

Treatment in the first group was started with HFNC, and in the second group was started with standard mask oxygen therapy and salbutamol nebulisation. If the expected response was not achieved by the end of the second hour, salbutamol nebulisation was added to HFNC in the first group, or HFNC was added to salbutamol in the second group. Support with HFNC was not removed when placing the jet nebuliser face mask, in patients requiring a change in therapy. The PED physician deemed a treatment change was required; if RCS scores of the patient were not decreased by at least two points, or increased above baseline, and/or if a downward change in the clinical severity category was not achieved and/or if there was further decrease or no improvement in SpO_2 measurements, or if the patient showed obvious non-compliance with the treatment. After commencing the trial,

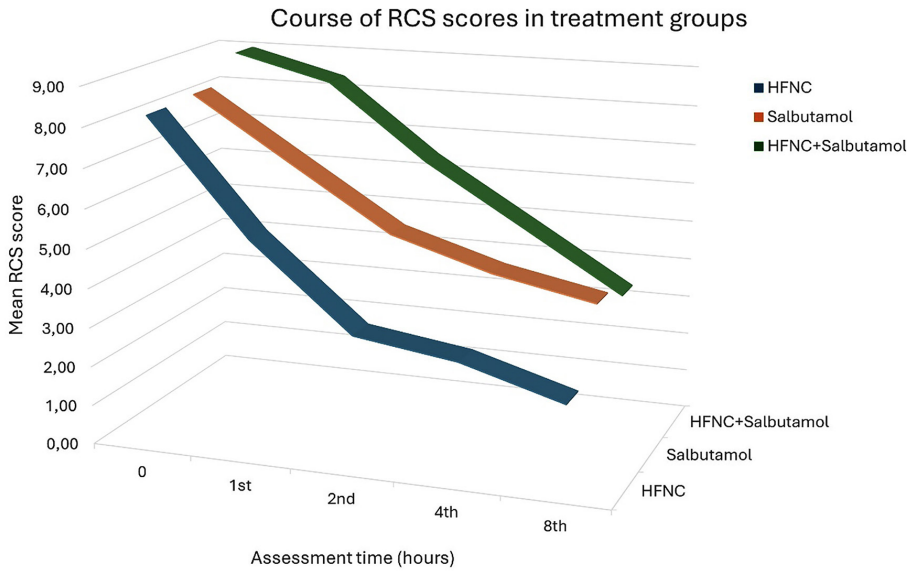

Figure 1. Course of RCS scores in treatment groups
RCS: Respiratory clinical score, HFNC: High-flow nasal cannula oxygen therapy system

Respiratory clinical scoring tool			**Assessment time (hour)**				
Variables	**Features**	**Points**	**0**	**1st**	**2nd**	**4th**	**8th**
Respiratory rate/min	<30	0					
	≤45	1					
	≤60	2					
	>60	3					
Retractions	None	0					
(Work of breathing)	Subcostal OR intercostal	1					
	At least 2 of them subcostal/intercostal/substernal OR nazal flaring	2					
	At least 3 of them subcostal/intercostal/substernal/suprasternal/ supraclavicular OR nazal flaring/head bobing	3					
Dyspnea	Normal feeding vocalizations and activity	0					
(Shortness of breath)	Any of them difficulty feeding decreased vocalization OR agitated	1					
	At least 2 of them difficulty feeding decreased vocalization OR agitated	2					
	Any of them stops feeding no vocalization drowsy OR confused	3					
Wheezing	None	0					
	End-expiratory wheeze only	1					
	Long lasting OR whole expiratory wheeze	2					
	Inspiratory and expiratory wheeze OR diminished breath sounds OR both	3					
Total RCS score*	Time 0: 1st: 2nd:	4th:	8th:				
Heart rate/min**	≤150	0					
	≤160	1					
	≤170	2					
	>170	3					
Saturation SpO_2 %**	≥95	0					
	≥94	1					
	≥90	2					
	<90	3					

*: Based on the total score obtained there can be 3 clinical categories of respiratory distress Mild (0-4) Moderate (5-8) Severe (9-12)
**: Heart rate and saturation SpO_2 are evaluated separately apart from scoring

RCS scores were evaluated at 0, 1, 2, 4, and 8 hours, along with hourly vital signs and SpO_2% measurements of the patients.

Implementations and Protocols

HFNC therapy

Heated and humidified HFNC oxygen is delivered via Airvo 2 device, through an Optiflow junior infant size cannula (OPT316) of Fisher & Paykel Healthcare. Initial settings were 2 L/kg/min flow and 100% inspiratory oxygen fraction (FiO_2); then, according to physician's clinical judgement, flow rate increments of 2 L/min (to a maximum of 25 L/min) were made at quarter-hour intervals and FiO_2 titrated to ≤40% to maintain SpO_2 ≥95%. All patients received standard care at the discretion of PED physicians. To wean the treatment, patients who achieved RCS <4 points for at least 8 hours under HFNC therapy underwent a gradual reduction of the flow rate by 10-25%. They were monitored for 2 hours after each change. If the infant was clinically stable and able to maintain saturations ≥95% for at least 2 hours after the flow rate decreased below 4 L/min, HFNC therapy was ceased and the patient was switched to low flow oxygen therapy with a mask. Oxygen support was turned off completely once a patient receiving standard oxygen therapy with a mask remained stable and maintained SpO_2 ≥95% for at least four hours.

Salbutamol treatment

Salbutamol was given 0.15 mg/kg (maximum 2.5 mg/dose), every 4 hours at most, using the small-volume jet nebuliser via face mask with 5-10 L/min oxygen flow supplied to the device. Patients were given low-flow (5-10 L/min) oxygen support with a simple mask to maintain SpO_2 ≥95 between treatments.

COMFORT Behaviour Scale (CBS)

CBS is a measurement tool to assess pain, distress, and sedation in pediatric patients under a variety of respiratory supports. The CBS, scored out of 30 points in total, indicates optimal patient comfort between 11 and 22 points; ≥23 points are interpreted as insufficient comfort, while ≤10 points indicate excessive sedation.[14-17] PED nurses assessed comfort, calmness, and tolerability of the patients during both HFNC and salbutamol nebulisation therapies within half an hour of initiating each treatment. The assessment was done once by a pre-trained nurse, who waited for 10-15 minutes for the child to get used to the environment and the practice. Total CBS was calculated by scoring 6 behavioural parameters, such as alertness, calmness/agitation, respiratory response, physical movement, muscle tone, and facial expression, assigning each a score of 1-5 points.

The physicians and nurses working in the PED were informed about the study protocol in advance and trained for scoring evaluation.

The history and examination findings of all patients at the time of admission; hourly temperature, saturation, heart rate, blood pressure, and respiratory rate; and the RCS scores calculated at 0-1-2-4-8 hours of the treatment were recorded on the prepared forms. CBS points, as well as any side effects, problems, and complications observed during the treatments, were also recorded. The patients' file records were accessed, and respiratory viral agents, laboratory results (haemogram, blood gases, C-reactive protein, procalcitonin, blood electrolytes, and glucose), and history of recurrent bronchiolitis in clinical follow-up, which were available, were recorded on the data collection forms. The length of stay in hospital and intensive care unit was recorded. Patients were contacted by telephone within the first 7 days after discharge and asked about persistence of symptoms and any history of readmission to the hospital or PED within a few days.

Statistical Analysis

Based on previous studies we estimated treatment failure rates of different modalities were 7-20% in infants with bronchiolitis.[4] An unequal distribution of a sample size involving 72 infants is necessary to have ≥80% power at a 5% significance level to assess the difference between two treatment modalities (Suresh KP, Chandrashekara S. Sample size estimation and power analysis for clinical research studies. J Hum Reprod Sci 2012;5:7-13).

SPSS V.23 was used for data entry; continuous data were presented as mean and standard deviation (SD) or median and interquartile range (IQR) depending on variable distribution; categorical data were presented using number and percentage. X^2, Mann-Whitney U test, dependent sample t-test, Spearman's rho pairwise correlation analyses, related samples Freidman's Two-Way Analysis and Kruskal-Wallis test and One-Way ANOVA test with applying Bonferroni adjustment of repeated measurements were used in the comparisons between the treatment groups according to the characteristics of the variables with a significant p-value <0.05.

Results

Seventy-two children who were followed up in the emergency department of a university hospital, which has an annual admission of 45,000 pediatric patients, between 01.10.2018 and 31.03.2019 and who met the criteria were included in the study. A total of 229 eligible patients with acute bronchiolitis were identified during this period. Of these, 157 were excluded due to RCS <4 points, recurrent bronchiolitis,

the presence of other comorbidities, or family refusal (summarized in Figure 2).

Of the 72 patients included in the study, 59.7% were under 6 months at admission, and their mean age was 7.8±0.4 months. The whole study group was evaluated altogether, the mean initial RCS was 8.42±2.02 points, and half of the patients were considered to have bronchiolitis with serious clinical severity (RCS>8). A significant decrease in the mean RCS scores of the patients was observed within hours under treatment (6.82±1.92, 5.13±2.20, 4.28±2.29, 3.58±2.37 points at 1, 2, 4, and 8 hours, respectively) (p<0.05). A decrease of at least 2 points from the baseline was achieved in RCS scores at the second and fourth assessment hours in 85.3% and 98.5% of the patients, respectively. 51.4% of the patients were hospitalised in the ward and 4.2% in the intensive care unit. No patient died in the study group. The mean length of hospital stay was 70±64.6 hours; 50% of the patients were readmitted to PED with respiratory complaints within the first few days following discharge; and 59.7% had bronchiolitis again in the 20-month follow-up. Children who were readmitted to PED or hospital in the early period had recurrent episodes of bronchiolitis during follow-up (p=0.002).

The initial treatment groups [HFNC (HF) and salbutamol+mask oxygen (S)] were similar in terms of socio-demographic and clinical characteristics except that a higher proportion of children in the HFNC group came from crowded families (p=0.014). Socio-demographic characteristics and clinical and laboratory findings of the initial treatment groups are given in Tables 1a and 1b.

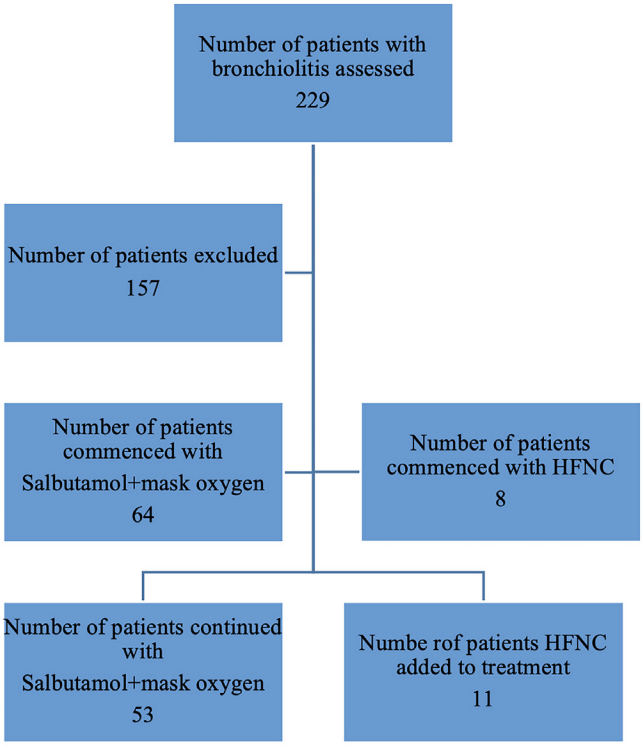

Figure 2. A flowchart showing numbers of patients assessed, excluded from the study and included into treatment groups
HFNC: High-flow nasal cannula oxygen therapy system

The mean heart rate of the patients decreased below 150 beats/min, which is the tachycardia limit value in children under 2 years of age, and the mean respiratory rate decreased below 50/min, which is the tachypnoea limit value, at the 1st hour in the HF group and after the 4th hour in the S group.[18] HFNC had to be added to the treatment, in 17.1% of those whose treatment was started with salbutamol plus mask oxygen, whereas no treatment change was required in any patient in the HFNC group. Among the patients in group S, those who required HFNC, 90.9% were older than 6 months, 81.8% had a baseline RCS >10 points, and 72% had hypoxia in blood gases. Having older patients' age (p=0.00), higher RCS scores at 1st and 2nd hours (p=0.001 and 0.025), wheezing at 2nd hour (p=0.003), and higher retraction scores at 1st to 4th hours (p=0.005 and 0.02) made a significant difference in terms of treatment change. The courses of clinical characteristics and outcomes of patients in three treatment groups are given in Tables 2a-d. Patients who were initially treated with HFNC

Table 1a. Socio-demographical features of initial study groups

Parameter	HFNC (n=8) n (%)	Salbutamol (n=64) n (%)	p-value
Gender			
Female	3 (37.5)	22 (34.4)	
Male	5 (62.5)	42 (65.6)	1
Age (months)			
0-3	2 (25)	17 (26.6)	
4-6	1 (12.5)	23 (35.9)	
7-12	2 (25)	14 (21.9)	
13-24	3 (37.5)	10 (15.6)	0.385
Prematurity <36 weeks	2 (25)	13 (20.3)	0.669
Caesarean birth	7 (87.5)	45 (70.3)	0.429
Respiratory support in neonatal period	2 (25)	10 (15.6)	0.613
Exclusive breast feding for the first 6 months	4 (50)	43 (67.2)	0.436
Regular prophylactic use of vitamin D	5 (62.5)	53 (86.9)	0.106
Age-appropriate vaccination	7 (87.5)	64 (100)	0.111
Care in a day-care center	0 (0)	6 (9.4)	1
History of food allergy/eczema in child	2 (25)	10 (15.6)	0.613
Family history of asthma	4 (50)	24 (37.5)	0.703
Smoking history at home	5 (62.5)	34 (53.1)	0.719
Crowded family environment	6 (75)	18 (28.1)	0.014
Low economical level	0 (0)	13 (20.3)	0.336

HFNC: High-flow nasal cannula oxygen therapy system

and took the (HF+S) treatments were evaluated together (15/19 patients, 79%); it was observed that more patients were hospitalized from this group (p=0.017) than from the S group (25/53 patients, 48%). Length of hospital stay was significantly longer in patients whose treatment was started with HFNC and/or had HFNC (p=0.002). In 3 patients younger than 2 months, hospitalized in the pediatric intensive care unit, 2 of whom were male, the RCS were 9 and 10, and one of them was followed under HFNC. Two of the three patients who were discharged after 72-168 hours of follow-up returned to PED in the early period; both were in the salbutamol group. Readmission to PED was significantly higher in the salbutamol group because of persistent complaints in the first few days after discharge (p=0.00). No complications related to treatment interventions were observed in any patient in the study groups.

Table 1b. Clinical and laboratory findings of initial study groups

Parameter	HFNC (n=8) n (%)	Salbutamol (n=64) n (%)	p-value
Complaints at admission			
Cough	6 (75)	43 (67.2)	
Respiratory distress	2 (25)	16 (25)	
Fever and the others*	0 (0)	5 (7.8)	1
Examination findings at admission			
Fever >38 °C	3 (37.5)	9 (14.1)	0.123
Tachypnoea >50/min	5 (62.5)	49 (76.6)	0.404
Tachycardia >150/min	6 (75)	48 (75)	1
Desaturation <95%	2 (25)	14 (21.9)	1
Dyspnoea	8 (100)	59 (92.1)	(0.658)
Retractions	8 (100)	60 (93.7)	0.764
Wheezing	8 (100)	62 (97.9)	0.063
Others**	2 (25)	9 (14.1)	0.412
Laboratory findings at admission* **			
Anemia <10 gr/dL	1 (14.3)	17 (27.9)	0.666
Leukocytosis >15.000/mm^3	1 (14.3)	12 (19.7)	0.706
CRP >2 mg/dL	1 (12.5)	9 (14.1)	0.836
Acidosis (pH <7.35)	1 (12.5)	13 (22)	0.518
Hypercarbia (pCO_2>45 mmHg)	0 (0)	5 (8.5)	0.462
Respiratory clinical score at admission			
4-8 points	6 (75)	31 (48.4)	
9-12 points	2 (25)	33 (51.6)	0.262
Comfort behaviour score (n=33/72 45.8%)			
Over-sedation 10 points	3 (37.5)	6 (24)	
Optimal comfort 11-22 points	5 (62.5)	15 (60)	
Inadequate comfort 23 points	0 (0)	4 (16)	0.429

*: Diarrhea vomiting söre throat runny nose, **: Rales dehydration increased anterior-posterior chest diameter oropharyngeal hyperemia tonsillar hypertrophy plus postnasal serous discharge, ***: Venous blood gasses were obtained in 67/72 patients (93%) hemogram was obtained in 68/72 patients (94%), HFNC: High-flow nasal cannula oxygen therapy system, CRP: C-reactive protein

The mean CBS score evaluated in a total of 33 children was 13.9±5.1 points, indicating the optimal comfort level (between 11-22 points) in 60.6% of those examined. It was not applied to all patients because pre-trained nurses were not on duty or the PED was overcrowded and the evaluation period had passed. CBS did not differ according to patients' age, clinical disease severity, initial RCS scores, and treatment modalities (mean ± SD, min-max CBS: 18-6, 4.64±12.13 points in HF group and 24-7, 5.25±14.56 points in S group, p=0.330) of the patients (p>0.05).

Discussion

In this single-centre prospective clinical intervention study, we compared the effects of HFNC with nebulised bronchodilator and standard oxygen therapy, on the clinical course of infants, mostly younger than 6 months, in our emergency department follow-up presenting with a first episode of bronchiolitis of moderate to severe clinical severity Prospective hourly follow-up for 8 hours in PED, and re-evaluated with objective clinical scoring are the strengths of the study. As a weakness of the study, due to the small number of participants, results should be interpreted with caution.

RCS scoring has been defined as a reliable tool.[11] In this sense, with repeated examinations, the RCS may help the clinician to determine the severity of bronchiolitis, need for hospitalisation, follow-up of treatment response, change, and or addition of treatment, and need for intensive care by providing non-invasive objective evaluation that is not based on clinical experience.[17] In the present study, patients were significantly relieved earlier in the HF group compared to the S group in terms of RCS scores, clinical severity category, heart rate, respiratory rate, wheezing, and chest retractions, which are indicators of respiratory distress in bronchiolitis. In this study, although the mean heart rate of the patients decreased below 150 beats/min, and the mean respiratory rate decreased below 50/min at the 1st hour in the HF group and after the 4th hour in the S group, the improvement in the mean heart rate from the first hour and in the mean respiratory rate only at the 8th hour was statistically significant in favour of the HF group. Consistent with these findings, in infants diagnosed with bronchiolitis and pneumonia who were treated with HFNC and did not need a change in treatment, many studies in the literature have emphasized that the clinical evaluation criteria for response to treatment include improvements in SpO_2% and S/F ratio, RCS from the first hour, and regression of tachycardia in the early period.[10,19-24] On the other hand, there are studies reporting that improvement in respiratory rates was achieved over a longer period ranging from 1 to 6 hours under HFNC treatment.[5,19-23] Although the present study was limited by a small number of patients, it may be

Table 2a. Course of RCS scores and heart and respiratory rates under treatment

Parameter	Treatment groups				
	Evaluation time	HFNC (n=8)	Salbutamol (n=53)	Salbutamol + HFNC (n=11)	p-value
		Mean ± SD (95% CI for mean)	Mean ± SD (95% CI for mean)	Mean ± SD (95% CI for mean)	
RCS score	0. hour	8.25±1.16 (7.28-9.22)	8.32±1.97 (7.78-8.87)	9.00±2.72 (7.17-10.83)	0.588
	1st hour	5.38±1.40 (4.20-6.55)	6.72±1.75 (6.23-7.20)	8.36±2.11 (6.95-9.78)	0.031
	2nd hour	3.25±1.03 (2.38-4.12)	5.13±1.86 (4.62-5.65)	6.45±3.32 (4.22-8.69)	0.006
	4th hour	2.88±1.55 (1.58-4.17)	4.36±2.11 (3.78-4.94)	4.91±3.23 (2.73-7.09)	0.008
	8th hour	2.13±1.95 (0.49-3.76)	3.85±2.24 (3.22-4.47)	3.36±3.00 (1.34-5.39)	0.002
RR/min	0. hour	57.0±13.0 (46.1-7.8)	61.8±13.4 (58.1-65.5)	62.7±12.8 (54.1-71.3)	0.595
	1st hour	47.3±15.1 (34.7-60.0)	56.4±11.6 (53.2-59.6)	56.8±11.3 (49.2-64.4)	0.134
	2nd hour	46.7±14.5 (34.5-58.9)	52.3±9.8 (49.5-55.0)	54.7±19.8 (41.3-68.0)	0.37
	4th hour	46.3±18.43 (30.96-61.79)	48.66±10.07 (45.88-51.44)	48.73±19.66 (35.52-61.94)	0.894
	8th hour	37.25±18.9 (21.4-53.0)	44.7±9.8 (41.9-47.4)	43.6±14.3 (43.0-53.2)	0.263
HR/min	0. hour	161.8±14.8 (149.4-174.2)	160.7±16.6 (156.1-165.2)	154.6±44.6 (124.6-184.6)	0.702
	1st hour	142.5±15.2 (129.7-155.2)	158.2±16.9 (153.5-162.9)	145.1±49.7 (111.7-178.6)	0.053
	2nd hour	142.8±27.6 (119.8-165.9)	158.4±21.0 (152.5-164.2)	148.3±25.4 (131.2-165.4)	0.113
	4th hour	133.5±22.2 (114.9-152.0)	151.7±18.0 (146.7-156.7)	135.6±21.6 (121.0-150.1)	0.006
	8th hour	119.0±23.2 (99.6-138.4)	142.5±15.8 (138.2-146.9)	126.1±23.2 (110.5-140.8)	0

RCS: Respiratory clinical score, RR: Respiratory rate, HR: Heart rate, HFNC: High-flow nasal cannula oxygen therapy system, CI: Confidence interval, SD: Standard deviation

said that the clinical severity in infants with a first attack of bronchiolitis was relieved more rapidly with HFNC. Similarly, in a systematic review study which embraces 14 research articles on HFNC usage in pediatric emergency setting, Yurtseven et al.[24] reported that HFNC therapy was better than standard oxygen therapy and was at least as effective as other supports of non-invasive ventilation.

When the entire study group was evaluated together, 85.3% and 98.5% of the patients had at least a 2-point decrease in the mean RCS score at the second and fourth assessment hours, respectively, compared to the baseline. In addition, a significant difference was found in the mean RCS scores of the HF and S treatment groups from the 2nd hour onwards. In this respect, it is reasonable to conclude that in infants with moderate to severe bronchiolitis, it is rational and guiding to assess treatment failure, modifications, and the need for additional treatment (excluding clinical deterioration). This assessment can be conducted at the 2nd hour at the earliest based on the RCS score after the initiation of treatment. In a prospective pilot study, Mayfield et al.[5] compared HFNC with standard oxygen therapy in infants under 1 year of age with bronchiolitis, with one quarter of the infants in both groups receiving salbutamol therapy simultaneously. They reported that in patients who did not respond to treatment, heart rate and respiratory rate were significantly higher at 3 hours, with an increasing trend in respiratory rate >50/min, and heart rate >150/min.[10] Similarly, in a multicentre prospective randomised study, tachycardia, tachypnoea, persistent and gradually increased oxygen requirements between the 2nd and 3rd hours of follow-up were taken as criteria in determining treatment failure and the need for additional treatment.[25] In another study from Türkiye, the presence of persistent tachypnoea and tachycardia after the second hour in patients who did not respond to treatment was highlighted.[25]

In the study group, 15.2% of the patients required treatment modification because the expected improvement was not achieved. Although all of the patients whose treatment was changed were in the S group (17.1%), the difference between the groups did not reach statistical significance due to the small number of patients in the HF group. Patients who underwent treatment change had significantly higher scores for RCS points, wheezing, and retraction at the 2nd assessment hour and afterwards. Consistent with this, a multicentre prospective randomised controlled PARIS study

Table 2b. Course of RCS sub parameters under treatment						
Parameter	**Evaluation time**		**HFNC (n=8)**	**Salbutamol (n=53)**	**Salbutamol + HFNC (n=11)**	**p-value**
			n (%)	**n (%)**	**n (%)**	
Retraction	0. hour	Mild	1 (12.5)	16 (30.2)	1 (9.1)	0.322
		Moderate-severe	7 (87.5)	37 (67.8)	10 (90.9)	
	1st hour	Mild	3 (37.5)	25 (47.2)	1 (9.1)	0.061
		Moderate-severe	5 (67)	28 (52.8)	10 (90.1)	
	2nd hour	Mild	7 (87.5)	39 (73.6)	3 (27.3)	0.004
		Moderate-severe	1 (12.5)	14 (26.4)	8 (72.7)	
	4th hour	Mild	7 (87.5)	43 (81.1)	4 (36.4)	0.009
		Moderate-severe	1 (12.5)	10 (18.9)	7 (83.6)	
	8th hour	Mild	0	45 (84.9)	7 (63.6)	0.121
		Moderate-severe	8 (100)	8 (15.1)	4 (37.4)	
Dyspnoea	0. hour	Mild	3 (37.5)	20 (37.7)	2 (18.2)	0.509
		Moderate-severe	5 (62.5)	33 (62.3)	9 (81.9)	
	1st hour	Mild	7 (87.5)	26 (49.1)	4 (36.4)	0.075
		Moderate-severe	1 (12.5)	27 (50.9)	7 (63.6)	
	2nd hour	Mild	7 (87.5)	35 (66)	7 (63.6)	0.508
		Moderate-severe	1 (12.5)	18 (34)	4 (37.4)	
	4th hour	Mild	7 (87.5)	38 (71.7)	8 (72.7)	0.824
		Moderate-severe	1 (12.5)	15 (28.3)	3 (27.3)	
	8th hour	Mild	7 (87.5)	41 (77.4)	9 (81.8)	1
		Moderate-severe	1 (12.5)	12 (23.6)	2 (18.2)	
Wheezing	0. hour	Mild	3 (37.5)	8 (15.1)	2 (18.2)	0.317
		Moderate-severe	5 (62.5)	45 (84.9)	9 (81.8)	
	1st hour	Mild	5 (62.5)	24 (45.3)	2 (18.2)	0.129
		Moderate-severe	3 (37.5)	29 (54.7)	9 (81.8)	
	1st hour	Mild	8 (100)	39 (73.6)	7 (63.6)	0.02
		Moderate-severe	0	14 (27.4)	4 (37.4)	
	2nd hour	Mild	8 (100)	40 (75.5)	5 (45.5)	0.479
		Moderate-severe	0	13 (24.5)	6 (54.5)	
	4th hour	Mild	8 (100)	41 (77.4)	10 (90.9)	0.509
		Moderate-severe	0	12 (23.6)	1 (9.1)	

Mild takes 0 OR 1 points, Moderate-severe takes 2 OR 3 points. RCS: Respiratory clinical score, HFNC: High-flow nasal cannula oxygen therapy system

comparing HFNC and nasal low-flow oxygen treatments in infants with bronchiolitis under one year of age showed that treatment failure was twice as high in the standard nasal oxygen group (12% vs. 23%). Persistent tachycardia (56% and 69%), tachypnoea (72% and 76%), and high clinical assessment scores (77% and 78%) were found in both groups in a significant proportion of patients requiring treatment change. Franklin et al.[22] reported that successful results were obtained in 62% of patients switched from standard treatment to HFNC. This literature supports the results that there was no need to switch to another advanced treatment or intensive care unit admission for patients in our study group who received HFNC as part of their treatment modification.

The whole study group was evaluated together. The mean hospital stay of the patients was found to be 70 hours, which is similar to the literature.[26-28] However, patients in the present study whose treatment was started with HF and then continued with additional HF were hospitalised at a significantly higher rate and stayed in hospital for longer periods, as recently reported in a multicenter prospective study.[29] Although some reports on the use of HFNC at home have begun to be included in literature recently, the safety of home use is controversial.[30-33] Another issue that has not been fully clarified in HFNC therapy is the weaning protocol. As applied in our hospital, the recommendations in the literature include stepwise, controlled tapering schemes spread over extended hours. These rationales may explain

Table 2c. Patients' outcomes and course of clinical respiratory severity categories under treatment

Parameter	Evaluation	HFNC (n=8)	Salbutamol (n=53)	Salbutamol + HFNC (n=11)	p-value
		n (%)	n (%)	n (%)	
Clinical respiratory severity category*	0. hour				
	Moderate	6 (75)	28 (52.8)	3 (27.3)	0.12
	Severe	2 (25)	25 (47.2)	8 (72.7)	
	1st hour				
	Mild	1 (12.5)	2 (3.8)	0 (0)	0.001
	Moderate	7 (87.5)	44 (83)	4 (36.4)	
	Severe	0 (0)	7 (13.2)	7 (63.6)	
	2nd hour				
	Mild	4 (50)	12 (22.6)	3 (27.3)	0.034
	Moderate	4 (50)	39 (73.6)	4 (36.4)	
	Severe	0 (0)	2 (3.8)	4 (36.4)	
	4th hour				
	Mild	5 (62.5)	23 (43.4)	4 (36.4)	0.195
	Moderate	3 (37.5)	30 (56.6)	6 (54.5)	
	Severe	0 (0)	0 (0)	1 (9.1)	
	8th hour				
	Mild	6 (75)	29 (55.8)	6 (54.5)	0.332
	Moderate	2 (25)	23 (44.2)	4 (36.4)	
	Severe	0 (0)	0 (0)	1 (9.1)	
Patients' outcome in PED	Hospitalized	2 (25)	28 (52.8)	2 (18.2)	0.062
	Outpatient	6 (75)	25 (47.2)	9 (18.8)	
Re-admission to PED	Yes	0	34 (64.2)	2 (18.2)	0

*: Mild: Takes 0-4 points, Moderate: takes 5-8 points, Severe: Takes 9-12 points, PED: Pediatric emergency department, HFNC: High-flow nasal cannula oxygen therapy system

Table 2d. Patients' treatment times

Parameter	Treatment groups			p-value
	HFNC (n=8)	Salbutamol (n=53)	Salbutamol + HFNC (n=11)	
	Mean ± SD (95% CI for mean)	Mean ± SD (95% CI for mean)	Mean ± SD (95% CI for mean)	
Length of hospital stay, hours	97.0±58.3 (48.1-145.8)	56.2±59.0 (39.9-72.5)	116.7±71.6 (68.5-164.8)	0.007
Duration of oxygen uptake, hours	97.0±58.3 (48.1-145.8)	54.9±57.7 (39.0-70.8)	107.6±66.9 (62.6-152.6)	0.012

HFNC: High-flow nasal cannula oxygen therapy system, SD: Standard deviation, CI: Confidence interval

the higher rate and longer duration of hospitalization of the patients in the HF group.[8,34-38] However, due to presence of a very wide distribution range and large SD necessitate careful interpretation of the comparison results for length of hospital stay.

In the present study group, 50% of the patients presented to the PED again with respiratory complaints within the first few days following discharge. There was no difference between patients whose treatment was continued at home (47.5%) and those who were hospitalised (42.5%) in terms of readmission to PED. The fact that one third of the study group consisted of infants younger than 3 months and more than half of them were boys, as well as the fact that one out of every two infants was exposed to smoking at home, may explain the high rate of readmission to the emergency department. In addition, families may have been more concerned about their previously healthy infants who had their first episode of bronchiolitis. We did not evaluate the outcome of re-visits to PED in our study. In our study group, HFNC therapy seemed to be significantly advantageous in terms of the need for readmission to PED. In the literature, return visits to the hospital within 3 to 30 days following discharge in children who were

hospitalized and treated for acute bronchiolitis, or whose treatment was continued at home after observation in the emergency department, have been reported as 23.8-34.2%. Readmissions to the hospital have been reported as 3.7-8%, respectively. It was emphasized that most of the return visits were due to prolonged recovery from bronchiolitis rather than clinical worsening. Also, supporting present study findings, it has been demonstrated that factors such as age <3 months, male sex, respiratory syncytial virus positivity, and exposure to cigarette smoke may increase the risk for readmission to PED and re-hospitalisation in infants with bronchiolitis.[39-44]

Acute bronchiolitis shows a course in which the most intense symptoms are seen in the first 3-4 days, gradually decreasing and mostly improving in 7-14 days.[39,45] Patients in group S, who had a shorter duration of inpatient hospitalisation, may have returned to PED with respiratory complaints during the period spent at home. However, it has also been reported in the literature that the number of days of inpatient treatment has no effect on the frequency of readmission.[45] On the other hand, there may be a difference due to the small number of patients in group HF. In this regard, evaluation based on the study group's data would be insufficient and is a limitation.

The CBS of the initial treatment modalities did not differ statistically in the present study, which may be another restriction due to the number of patients. In a recent study, it was reported that comfort and satisfaction in children with bronchiolitis were greater with HFNC,[46] as observed by both nurses and parents. However, in detail, median CBS scores in those groups (13, IQR 9-15 vs. 17, IQR 13-23) both indicate optimal comfort levels as observed in our present study.

Study Limitations

Although the results show that HFNC treatment provides rapid clinical improvement in infants with first acute bronchiolitis, the small number of participants is a limitation of this study. Constraints of the study budget limited the number of patients in the HFNC treatment group. The small sample size in the HFNC group is the main weakness of this study that might diminish statistical power and affect the interpretation of the results.

Conclusion

With the results of this study, which was evaluated on a limited number of patients, it may be said that HFNC seems effective and reliable in addressing dyspnea and retraction findings associated with increased workload. It produces earlier and faster clinical improvement measured by RCS than S in infants presenting with the first episode of acute bronchiolitis with moderate to severe clinical severity. It reduces return visits to PED related to the same disease. However, it seems to be disadvantageous in terms of longer hospital stay. There is a need for studies with large-scale groups regarding the shortening of hospital stay, trials on faster weaning protocols, and/or the applicability of HFNC treatment at home.

Ethics

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Also, the study was approved by the Local Clinical Researches Ethics Committee of Akdeniz University (15.11.2017-674).

Informed Consent: Informed written consent was obtained from a parent of each child.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.Z.G.D., Ö.T.K., N.E., Ö.B., R.G., Concept: Ö.T.K., N.E., Design: Ö.T.K., N.E., Data Collection or Processing: Ş.Z.G.D., Ö.T.K., N.E., Ö.B., R.G., Analysis or Interpretation: Ş.Z.G.D., Ö.T.K., N.E., Ö.B., R.G., Literature Search: Ş.Z.G.D., Ö.T.K., N.E., Writing: Ö.T.K., N.E.

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