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Original Article

Paediatrics Section

Efficacy of Oxygen Delivered through High Flow Nasal Cannula versus Non Rebreathing Mask in Infants with Mild and Moderate Bronchiolitis: An Open-labelled Randomised Controlled Trial

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ABSTRACT

Introduction: Bronchiolitis accounts for substantial portion of infant and paediatric hospital admissions worldwide. High flow nasal cannula is a relatively new, safe, comfortable and well tolerated mode of oxygen delivery for infants and children presenting with respiratory distress in emergency units and general wards.

Aim: To compare the efficacy of oxygen delivered through high flow nasal cannula with non rebreathing mask in infants with mild and moderate bronchiolitis.

Materials and Methods: This open-labelled randomised controlled trial was conducted among 80 infants under 12 months of age admitted with mild and moderate bronchiolitis in the well-equipped Paediatric Wards of Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India, from January 2017 to August 2018. Eligible recruited infants were randomised into two groups. First group receiving oxygen through Non Rebreathing Mask (NRM group) and second group receiving oxygen through High Flow Nasal Cannula (HFNC group). All the participants were followed-up with clinical examinations and investigations and outcomes were noted. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) software, Chi-square test and student's t-test used, p-value <0.05 was considered as statistically significant.

Results: There was a significant reduction in duration of oxygen required in the HFNC group (mean duration in hours: 13.98±6.612) when compared to NRM group (mean duration in hours: 26.70±4.81). The mean length of hospital stay was lesser in HFNC group (3.65±1.460 days) when compared to NRM group (5.35±1.657 days). Comparison of heart rate between the two groups showed a statistically significant decrease in mean heart rate (144.0±7.2) as early as 2 hours (p-value 0.010) after initiation of HFNC when compared to NRM group (148.1±6.5). respiratory rate was significantly reduced when compared from 2 hours (p-value <0.001) of initiation of intervention, with HFNC group showing higher percentage of reduction in respiratory rate than NRM group. Mean SpO_2 levels were higher in HFNC group when compared to NRM group at various time intervals, though not significant statistically.

Conclusion: High flow nasal cannula, under monitoring, could safely be used in paediatric wards in infants and children with mild and moderate bronchiolitis.

Keywords: Duration of oxygen, Length of hospital stay, Mode of oxygen delivery, Paediatric wards, Respiratory distress

INTRODUCTION

Bronchiolitis, acute lower airway lung disease, accounts for substantial portion of hospital admissions and morbidity in infant and paediatric population all over the world [1]. Over the last decade, there is a change in trend in the management of Bronchiolitis from invasive to a non invasive one and latest addition in the respiratory management of bronchiolitis is the use of High Flow Nasal Cannula [HFNC] [1]. Since the introduction of HFNC, a significant reduction in invasive ventilation in bronchiolitis cases has been demonstrated. HFNC was first used in intensive care units and was more restricted to preterm infants and neonates [2]. Its use in emergency room and paediatric wards has been more recent and is mainly applied in mild and moderate bronchiolitis [2].

The striking advantage of HFNC is its simple application and minimal interference with patient comfort. Range of indications for HFNC use has broadened including respiratory, cardiac, neuromuscular diseases and there is a need for sufficient evidence based studies for the same [3]. However, the evidence for safety and effectiveness of HFNC as a respiratory support in children is relatively deficient, as shown by two Cochrane reviews [4,5].

Most of the studies being retrospective [1,3,4,6] this Randomised Controlled Trial (RCT) was undertaken to search for a stronger evidence about the efficacy and safety of HFNC in paediatric wards.This study was aimed at comparing the efficacy of HFNC vs oxygen through Non Rebreathing Mask (NRM) in infants and children with mild and moderate bronchiolitis.The primary outcome measures were duration for which oxygen was required and length of hospital stay. The secondary outcome measures were haemodynamic parameters including mean heart rate, percentage reduction in heart rate, mean respiratory rate, percentage reduction in respiratory rate, mean difference in saturation levels, adverse events including Paediatric Intensive Care Unit (PICU) admission/ invasive ventilation- at admission and at various time intervals after initiation of treatment.

MATERIALS AND METHODS

This open-labelled randomised controlled trial was conducted in the well-equipped Paediatric Wards of Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India, from January 2017 to August 2018. Approval from ethical committee was obtained before start of study from the Institutional Ethical Board Committee-

Madras Medical College, Chennai [EC Reg no:ECR/270/Inst./TN/2013]. Informed consent was taken from every participant before enrolling them into study and confidentiality was maintained well throughout.

Sample size calculation: Based on a study by Ture E et al., comparing efficacy of HFNC with other face mask oxygen therapy, sample size was calculated using mean respiratory rate at 3rd hour for each intervention [7]. Mean respiratory rate at 3rd hour using oxygen through non rebreathing mask (mean1)=56.47±10.99, mean respiratory rate at 3rd hour in HFNC group (mean 2)=49.27±10.40.

The sample size was calculated considering the power of the study as 80% with a 95% confidence interval as:

$N=(Z_{\alpha/2}+Z_{\beta})^2\ [(SD_1)^2+(SD_2)^2]\div[\text{Mean 1-Mean 2}]$

Where, Mean1=56.47, Mean 2=49.27

$SD_1=10.99$, $SD_2=10.40$

$Z_{\alpha/2}=1.96$ at 95% CI, $Z_{\beta}=0.84$ at 80% power

N=34.6=35

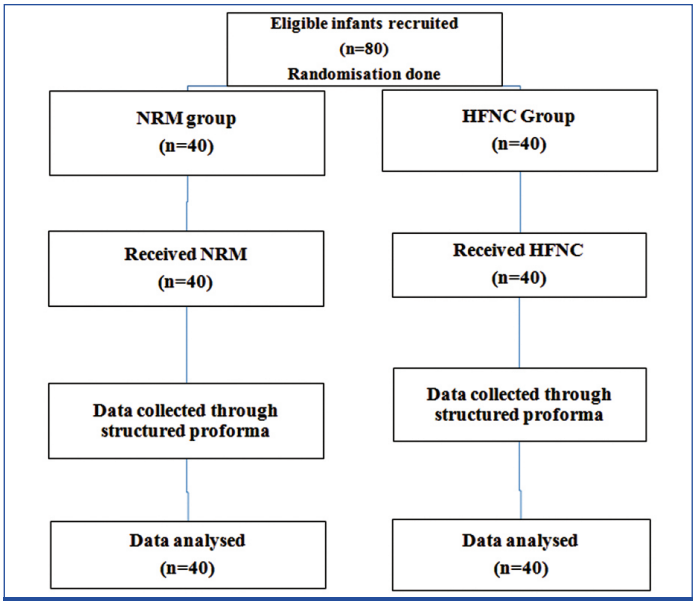
The estimated sample size by applying the 2 means with standard deviation was 35 in each arm. Hence, a total sample 80, 40 in each group was chosen for this study.

Inclusion criteria: All children aged less than 12 months with clinical diagnosis of mild and moderate bronchiolitis (graded based on Wood Downes Ferres scoring) [8], requiring oxygen support were included in the study.

Exclusion criteria: Children whose parents do not consent for the study, severe bronchiolitis, upper airway obstruction, craniofacial malformation were excluded from the study.

Study Procedure

A total of 80 infants fitting into the inclusion criteria were selected after obtaining parental consent. Recruited infants were randomised into two groups by computer generated random numbers with a block size of 8. Allocation concealment was done using sealed envelopes. Neither the clinicians nor the patients knew which group they were allocated to among the two groups [Table/Fig-1].



[Table/Fig-1]: CONSORT flowchart.

- **Non Rebreathing Mask (NRM) group:** First group was treated with conventional oxygen through non rebreathing mask at a flow rate of 2-10 L/minute (adjusted individually, upto 10 L/minute).
- **High flow nasal cannula (HFNC) group:** Second group was treated with HFNC 2 L/kg/minute, upto 10 kg, with an addition of 0.5 L/kg for each kilogram more than 10 kg.

The observed haemodynamic parameters were recorded [6].

A structured proforma was devised and circulated in Paediatric Wards. Doctors and staff nurses were oriented about the same for proper collection and documentation of data in the proforma. Data collected everyday was counter checked by principal investigator. Baseline characteristics of both groups including age, gender, family history of asthma, socio-economic status, immunisation history, any bad child rearing practices followed (administration of 'vasambu', gripe water), any contact with tuberculosis patients, presence of co-morbids including cardiac/airway anomalies were noted in the proforma [9]. Data including duration of oxygen therapy, length of hospital stay and various parameters including heart rate, respiratory rate, oxygen saturation were noted in the proforma at fixed times from initiation of intervention (on admission, 1, 2, 6, 12, 24, 36, 72, >72 hours) in both groups. Adverse events in terms of escalation of respiratory support like invasive mechanical ventilation or admission into intensive care unit or death was also noted.

STATISTICAL ANALYSIS

The collected data was analysed through Statistical Package for Social Sciences (SPSS) software version 21.0. Primary outcome was measured using Chi-square tests, and secondary outcomes were measured by student's t-test. A p-value <0.05 was considered significant.

RESULTS

Demographic details are presented in [Table/Fig-2]. Subjects in HFNC group needed significantly lesser duration of oxygen (13.98±6.612 hours) when compared to NRM group (26.70±4.81 hours). Subjects in HFNC group had roughly 2 days lesser hospital stay (3.65±1.460 days) than NRM group (5.35±1.657 days) [Table/Fig-3,4].

Parameters	NRM (n, %)	HFNC (n, %)	p-value
Age			
<3 months.	6 (15%)	9 (22.5%)	0.568
3-6 months	18 (45%)	14 (35%)	
>6 months	16 (40%)	17 (42.5%)	
Mean age (SD)=178.5 days (102.68)			
Gender			
Male	26 (51%)	25 (49%)	0.816
Female	14 (48.3%)	15 (51.7%)	
Family history of asthma			
Present	3 (7.5%)	4 (10%)	0.692
Absent	37 (92.5%)	36 (90%)	
Socio-economic status(Modified Kuppuswamy scale)			
Poor	2 (5%)	3 (7.5%)	0.850
Lower middle	29 (72.5%)	27(67.5%)	
Upper middle	9 (22.5%)	10 (25%)	
Bad child rearing practice			
Present	6 (15%)	8 (20%)	0.556
Absent	34 (85%)	32 (80%)	
Immunisation history			
As per schedule	38 (95%)	37 (92.5%)	0.644
Incompletely immunised	2 (5%)	3 (7.5%)	
Contact history (with tuberculosis patient)			
Present	1 (2.5%)	0	0.314
Absent	39 (97.5%)	40 (100%)	
Co-morbid illness			
Cardiac illness	2 (5%)	1 (2.5%)	0.207
Airway anomalies	8 (20%)	3 (7.5%)	

[Table/Fig-2]: Demographic profile of the study participants.
NRM: Non rebreathing mask; HFNC: High flow nasal cannula

Duration of oxygen therapy	Group NRM n (%)	Group HFNC n (%)	Total n (%)	Chi-square value p-value
<24 hours	4 (10)	35 (87.5)	39 (48.8)	p-value <0.001 χ^2=48.205
24-36 hours	34 (85)	5 (12.5)	39 (48.8)	
>36-48 hours	2 (5)	0	2 (2.5)	
Mean duration of oxygen therapy	26.70±4.81	13.98±6.162		

[Table/Fig-3]: Distribution of study groups according to duration of oxygen therapy.
p-value <0.05 was considered as statistically significant

Length of hospital stay	Group NRM n (%)	Group HFNC n (%)	Total n (%)	Chi-square value p-value
2 to 4 days	5 (12.5)	33 (82.5)	38 (47.5)	p-value <0.001 χ^2=39.298
>4 days	35 (87.5)	7 (17.5)	42 (52.5)	
Mean length of hospital stay	5.35±1.657	3.65±1.460		

[Table/Fig-4]: Distribution of the study groups according to length of hospital stay (N=80).
p-value <0.05 was considered as statistically significant (Chi-sqaure test)

Comparison of heart rate between the two groups showed a statistically significant decrease in mean heart rate (144.0±7.2) as early as 2 hours (p-value=0.010) after initiation of HFNC when compared to NRM group (148.1±6.5). Also the rate of decrease in heart rate was statistically significant (5.5% vs 4.5%) in HFNC group when compared to NRM group. Mean respiratory rate was significantly reduced from 2 hours of oxygen support in HFNC group (49.1±9.2) when compared to NRM group (54.8±5.6). Also, change in respiratory rate was significant when compared from 2 hours (p-value <0.001) of initiation of intervention, with HFNC group showing higher percentage of reduction in respiratory rate than NRM group. Mean SpO_2 levels were higher in HFNC group when compared to NRM group at various time intervals, though not significant statistically [Table/Fig-5-9].

Heart rate	NRM group (Mean±SD)	HFNC group (Mean±SD)	p-value
0 min	162.8±8.1	163.8±8.6	0.594
1 hour	155.4 ±7.2	154.7±6.4	0.648
2 hours	148.1±6.5	144.0±7.2	0.010
6 hours	139.1 ±7.8	132.9±8.5	0.001
12 hours	131.0±8.8	123.3±7.7	<0.001
24 hours	123.3±8.5	117.7±6.2	0.001
36 hours	119.3±7.7	114.9±5.3	0.004
48 hours	114.9±6.3	112.2±4.0	0.022
72 hours	111.7±5.3	109.9±3.8	0.082
>72 hours	109.5±4.7	108.4±3.3	0.193

[Table/Fig-5]: Comparison of mean heart rate of the study groups at various time intervals (N=80).
p-value <0.05 was considered as statistically significant (Student's t-test)

Reduction in heart rate	NRM group Mean (%)	HFNC group Mean (%)	p-value
1 hour	7.4 (4.5)	9.1 (5.5)	0.026
2 hours	14.7 (8.9)	19.7 (12.0)	<0.001
6 hours	23.8 (14.5)	30.9 (18.8)	<0.001
12 hours	31.8 (19.4)	40.6 (24.6)	<0.001
24 hours	39.5 (24.2)	46.1 (28)	0.002
36 hours	43.5 (26.6)	48.9 (29.7)	0.010
48 hours	47.8 (29.3)	51.6 (31.4)	0.051
72 hours	51.1 (31.3)	54.0 (32.8)	0.142
>72 hours	53.3 (32.6)	55.5 (33.7)	0.240

[Table/Fig-6]: Comparison of reduction of heart rate from baseline value, among the study groups at various time intervals (N=80).
p-value <0.05 was considered as statistically significant (Student's t-test)

Respiratory rate	NRM group (Mean±SD)	HFNC group (Mean±SD)	p-value
0 min	68.1±6.0	68.5±7.2	0.829
1 hour	60.9±5.7	58.9±6.2	0.139
2 hours	54.8±5.6	49.1±9.2	0.001
6 hours	49.0±6.8	43.1±5.5	<0.001
12 hours	43.6±6.4	37.4±5.2	<0.001
24 hours	39.7±5.7	34.1±4.6	<0.001
36 hours	35.7±3.8	32.0±4.6	<0.001
48 hours	33.8±3.6	30.0±4.0	<0.001
72 hours	31.3±3.0	28.6±3.8	0.001
>72 hours	29.7±3.0	27.1±3.7	0.001

[Table/Fig-7]: Comparison of mean respiratory rate of the study groups at various time intervals (N=80).
p-value <0.05 was considered as statistically significant (Student's t-test)

Reduction in respiratory rate	NRM group Mean (%)	HFNC group Mean (%)	p-value
1 hour	7 (10.6)	10 (13.8)	0.003
2 hours	13 (19.5)	19 (28.3)	<0.001
6 hours	19 (28.2)	25 (36.7)	<0.001
12 hours	25 (36.0)	31 (45.1)	<0.001
24 hours	28 (41.6)	34 (49.9)	0.002
36 hours	32 (47.3)	36 (53.0)	0.006
48 hours	34 (50.0)	38 (55.9)	0.010
72 hours	37 (53.8)	40 (58.0)	0.042
>72 hours	38 (56.1)	41 (60.3)	0.043

[Table/Fig-8]: Comparison of reduction of respiratory rate from baseline value, among the study groups at various time intervals (N=80).
p-value <0.05 was considered as statistically significant (Student's t-test)

SpO_2	NRM group (Mean±SD)	HFNC group (Mean±SD)	p-value
0 min	93.1±3.6	93.9±2.3	0.236
1 hour	95.6±3.1	96.5±1.3	0.108
2 hours	97.6±3.0	98.2±0.9	0.289
6 hours	98.1±3.1	98.8±0.9	0.131
12 hours	98.6±2.9	99.1±1.1	0.364
24 hours	98.6±2.6	98.6±0.9	0.862
36 hours	97.9±3.3	97.8±4.9	0.894
48 hours	97.9±3.1	98.5±1.0	0.245
72 hours	99.0±2.5	99.4±0.5	0.386
>72 hours	99.0±3.1	99.4±0.6	0.490

[Table/Fig-9]: Comparison of mean oxygen saturation (SpO_2) levels of the study groups at various time intervals (N=80).
p-value <0.05 was considered as statistically significant (Student's t-test)

Only one child in NRM group required intubation and only two in NRM group required ICU admission. All the three children improved and were discharged later. No death was encountered in both groups during the study.

DISCUSSION

During recent years, heated and humidified high flow nasal cannula as a respiratory support has become popular. The application of HFNC has led to more comfortable non invasive form of ventilation decreasing the need for invasive mechanical ventilation and its complications [3].

The present study found a significantly reduced duration of oxygen required in HFNC group (approximately 12 hours lesser) when compared with NRM group which is in par with a randomised control study conducted by Ergut AB et al,, in 60 patients with moderate and severe bronchiolitis, where duration of oxygen required was 56 hours in HFNC group when compared to 96 hours in NRM group [10].

In an observational study conducted by Milani GP et al., and retrospective study conducted by Reise J et al., length of hospital stay were significantly reduced in HFNC group compared to NRM group. This is consistent with this study showing significant reduction in length of hospital stay (2 days lesser) in HFNC group compared to NRM group [11,12].

The current study showed a significant reduction in mean heart rate and mean respiratory rate as early as 2 hours after initiation of HFNC when compared to NRM. Going through literature, Kallappa C et al., found that, after initiation of HFNC and NRM in subjects, there was a 20% reduction in heart rate from baseline in HFNC group much earlier than in NRM group [13] while Mckiernan C et al., also found that HFNC group had significant decline in mean respiratory rate compared to NRM group [14]. This current study could also identify responders and non responders to HFNC earlier (at 2 hours) as in par with study by Mayfield S et al., who could identify responders and non responders to HFNC within first hour of start of HFNC using mean heart rate and respiratory rate variations [1]. A systematic review concluded that HFNC had a positive clinical effect on SpO_2, PaO_2, respiratory rate and blood gas parameters in children with bronchiolitis [4].

Though in the present study, there was no significant difference in two groups in saturation levels, mean saturation levels at various time intervals were higher in HFNC group when compared to NRM group. This is consistent with a pilot study done by Hilliard TN et al., including 19 infants hospitalised with bronchiolitis, where a higher median SpO_2 at 8 hrs and 12 hrs, but not at 24 hrs, was found in the HFNC group than in a group receiving head-box oxygen [15]. Few other studies concluded that HFNC use was associated with an overall decline in need for intubation [3,10,16,17]. Wraight TI and Ganu SS, reported that 12% infants required step up CPAP or intubation when compared with 78% infants who successfully recovered with HFNC therapy [18]. However, Reise J et al., found no difference in intubation rate in both groups [12]. While previous studies suggest that HFNC has less treatment failures and decreases need for invasive ventilation, this could not be confirmed in the current RCT as in this study only one child in NRM group required invasive ventilation and treatment failures were not significantly different in both treatment groups. However, the present study observed a very obvious clinical improvement in HFNC group at a much earlier point in the course of treatment when compared with NRM group.

Infants who were started on HFNC experienced significant decrease in mean heart rate and mean respiratory rate as early as two hours of initiation of therapy. This in turn shows that HFNC reduces duration of oxygen required and need for invasive ventilation and its complications consequently leading to a decrease in length of hospital stay.

Limitation(s)

The limitation of this study is the fact that it was based on a single centre. Though this is a randomised controlled trial, a multicentric trial with a larger sample size would provide a stronger evidence.

CONCLUSION(S)

In conclusion, this study states that HFNC provides a safe, comfortable and well-tolerated means of respiratory support in infants and children with bronchiolitis in Paediatric Wards.In addition to rescue therapy, it can be used as a start up therapy as it reduces the duration of oxygen requirement and length of hospital stay. Also, need for invasive ventilation and its complications can be reduced.

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