Research Article

Comparative Study between Noninvasive Continuous Positive Airway Pressure and Hot Humidified High-flow Nasal Cannulae as a Mode of Respiratory Support in Infants with Acute Bronchiolitis in Pediatric Intensive Care Unit of a Tertiary Care Hospital

Mihir Sarkar, Rajasree Sinha, Satyabrata Roychowdhoury, Sobhanman Mukhopadhyay, Pramit Ghosh[1], Kalpana Dutta, Shibarjun Ghosh

Departments of Pediatrics and [1]Community Medicine, Medical College and Hospital, Kolkata, West Bengal, India

Abstract

Background: Early initiation of appropriate noninvasive respiratory support is utmost important intervention to avoid mechanical ventilation in severe bronchiolitis. **Aim:** This study aims to compare noninvasive continuous positive airway pressure (nCPAP) and hot humidified high-flow nasal cannulae (HHHFNC) as modes of respiratory support in infants with severe bronchiolitis. **Methods:** Prospective, randomized, open-label pilot study done in a tertiary-care hospital Pediatric Intensive Care Unit (PICU). Participants: 31 infants (excluding neonates) clinically diagnosed with acute bronchiolitis having peripheral capillary oxygen saturation (SpO_2) <92% (with room air oxygen); Respiratory Distress Assessment Index (RDAI) ≥11. Intervention: nCPAP (n = 16) or HHHFNC (n = 15), initiated at enrollment. Primary outcome: Reduction of need of mechanical ventilation assessed by improvements in (i) SpO_2% (ii) heart rate (HR); respiratory rate; (iii) partial pressure of carbon dioxide; (iv) partial pressure of oxygen; (v) COMFORT Score; (vi) RDAI from preintervention value. Secondary outcome: (i) total duration of noninvasive ventilation support; (ii) PICU length of stay; and (iii) incidence of nasal injury (NI). **Results:** Mean age was 3.41 ± 1.11 months (95% confidence interval 2.58–4.23). Compared to nCPAP, HHHFNC was better tolerated as indicated by better normalization of HR (P < 0.001); better COMFORT Score (P < 0.003) and lower incidence of NI (46.66% vs. 75%; P = 0.21). Improvements in other outcome measures were comparable for both groups. For both methods, no major patient complications occurred. **Conclusion:** HHHFNC is an emerging alternative to nCPAP in the management of infants with acute bronchiolitis.

Keywords: Acute respiratory failure, bronchiolitis, high-flow oxygen therapy, respiratory syncytial virus

Introduction

Bronchiolitis is an acute inflammatory injury of the bronchioles that is usually caused by a viral infection (most commonly by respiratory syncytial virus). Severe symptoms are more often seen in young infants.[1] Management is mainly supportive, includes proper hydration and moist oxygen support delivered through either face mask, nasal cannulae, noninvasive continuous positive airway pressure (nCPAP) or hot humidified high-flow nasal cannulae (HHHNFC). Severe cases may require mechanical ventilation (MV).[2-5]

nCPAP in bronchiolitis acts by widening the peripheral lung airways thus allowing the overdistended lungs in bronchiolitis to deflate. It also prevents the collapse of the poorly supported peripheral airways during expiration by increasing the airway pressure, thus increasing Functional residual capacity (FRC) which in turn increases gaseous exchange and hence oxygenation. A constant airway pressure during nCPAP support

Access this article online

Quick Response Code:

Website: www.ijccm.org

DOI: 10.4103/ijccm.IJCCM_274_17

Address for correspondence: Dr. Mihir Sarkar, Department of Pediatrics, Medical College and Hospital, 88, College Street, Kolkata - 700 073, West Bengal, India.
E-mail: drmihir09@gmail.com

How to cite this article: Sarkar M, Sinha R, Roychowdhoury S, Mukhopadhyay S, Ghosh P, Dutta K, *et al*. Comparative study between noninvasive continuous positive airway pressure and hot humidified high-flow nasal cannulae as a mode of respiratory support in infants with acute bronchiolitis in pediatric intensive care unit of a tertiary care hospital. Indian J Crit Care Med 2018;22:85-90.

maintains airway patency throughout the breath cycle, thus causing unloading of respiratory muscles and an improvement in breathing pattern.

Over the last decade, HHHFNC therapy has emerged as a new method to provide respiratory support for bronchiolitis.[6] Nasal cannulae, which were first used to administer supplemental oxygen (low-flow therapy) on a large scale, also showed the capability for the administration of nCPAP through HFNC as it developed. Needless to say, apart from meeting-specific physical criteria, a relative humidity of 100% and a temperature of 37°C are the basic requirements of this intervention.[7]

The application of HHHFNC in the Neonatal Intensive Care Unit and Pediatric Intensive Care Unit (PICU) has developed significantly during the last decade due to the fact that not only is this system capable of providing a specific percentage of the respiratory oxygen, but it can also administer noninvasive respiratory support of constant-flow CPAP without the need for any further equipment.[8]

When the respiratory disease is accompanied by increasing respiratory work, supportive mechanisms of HHHFNC are specifically categorized as follows:

Dead space ventilation in the nasopharyngeal space

High-flow therapy (HFT) may eventually enhance alveolar ventilation by decreasing the dead space through establishing washout in the nasopharyngeal space by gas insufflations (GIs), which in turn increases the minute ventilation.

Decrease in respiratory work

This is the result of providing some level of splinting in the nasopharynx, which has a significant ability of compliance. When HFT produces GIs beyond demand flow in the nasopharynx, it avoids the retraction of the nasopharynx wall in inspiration and with the lowering of resistance in this space; the respiratory work also decreases in inspiration. Moreover, during expiration, the expiratory flows face resistance in the nasopharynx and are redirected to the oropharynx, which eventually decreases the expiratory work because of the occurrence of the Coanda effect in the behavior of the gas.

Providing the maximum humidity and temperature

To establish optimal gas exchange, the airways increase the temperature and humidity of the inhaled gases to 37°C and 100%, respectively, while the HFT systems blocks energy wastage in the airways by establishing these conditions and eventually improving lung mechanics.

Study rationale

We conducted a prospective, randomized, pilot study involving patients admitted to the PICU with Bronchiolitis, complicated with acute hypoxemic respiratory failure to determine whether high-flow oxygen therapy as compared with noninvasive ventilation (NIV) therapy, could reduce the need of MV and improve outcomes.

Methods

Study design

We conducted a single-center, prospective, parallel group, open-label, and randomized pilot study at PICU of a tertiary care teaching hospital from September 2016 to February 2017. Approval was obtained from the institutional ethics committee. Informed written consent was obtained from at least one parent or a legal guardian before enrollment.

Participants

The inclusion criteria included (i) age 28 days to 12 months, i.e., infants excluding neonates; (ii) diagnosis of severe bronchiolitis consistent with clinical features (history of cough, prolonged expiration, tachypnea, retraction of the chest wall or grunting, wheezing, rales or rhonchi; supporting chest x-ray findings of hyperinflation); and (iii) fulfilling the criteria stating the need for nCPAP or HHHNFC, i.e., (peripheral capillary oxygen saturation [SpO_2] <92% mmHg breathing room air) and/or Respiratory Distress Assessment Index (RDAI) ≥11.[9] The SpO_2 of <92% breathing room air was chosen as a compromise between the severity of respiratory failure and patient safety during the study protocol.

Exclusion criteria were (i) emergency need for intubation; (ii) Glasgow Coma Scale <11; (iii) major acidosis (pH < 7.25); (iv) hypercapnia (partial pressure of carbon-dioxide [$PaCO_2$] >55 mmHg); (v) cough or gag reflex impairment; (vi) upper-airway obstruction; (vii) facial/gastric surgery; (ix) hemodynamic instability; and (x) uncorrected cyanotic congenital heart disease or pulmonary vascular anomalies.

Randomization and masking

Eligible patients were randomized using on-site computer-generated block randomization schedule to receive either nCPAP or HHHFNC.

Baseline data-collection

Sociodemographic variables (age, sex, and immunization status details) were recorded. During CPAP/HFNC treatment, all children were intensively observed by a trained nurse and thoroughly examined for respiratory and hemodynamic parameters such as body temperature, heart rate (HR), respiratory rate (RR), resting blood pressure (BP), and SpO2%.

RR was measured for a full minute and if fast (RR >50/min for <1 year),[9] it was remeasured and the two readings were averaged. Axillary temperature was measured using digital thermometer. Baseline SPO2% was measured using a pulse-oximeter with a probe on a finger or toe, in room air.

Baseline complete hemogram and chest X-ray were performed in all subjects at enrolment, as part of routine workup. As the study population is infants with severe bronchiolitis, who needed some respiratory support by nCPAP or HHHNFC and or RDAI ≥11, for this set of patients serial ABG is done as a part of routine care. Arterial line was done in the radial artery after modified Allen's test of randomized patients. Patency of arterial line was maintained with continuous heparin

infusion - @ 1–2 ml/h and concentration of 1 unit/ml. No complication was noted due to arterial line.[10] Blood samples were obtained aseptically using heparinized 1mL syringe, and blood gas analysis was done using automated ABG analyzer (OPTI CCA-TS Blood Gas Analyzer 2003, OPTI Medical, USA). Separate informed consent was taken from the parents for placement of arterial line.

Intervention

Infants were studied for either of the NIV modality under the study. Treatment sequence was assigned by randomization schedule generated on-site. Thus, 16 infants received nCPAP through a nasal mask (SERVO-i®, Maquet; Getinge Group, Sweden). CPAP was usually started at 4 cm H_2O and increased as necessary up to a maximum of 8 cm H_2O. Nasal prong or nasal mask (SERVO-i®, Maquet; Getinge Group, Sweden) of appropriate size which was snugly fitted and produces minimum leak and maximum comfort was used as interface.

Fifteen infants received oxygen through HHHFNC (AIRVO™ 2, Fisher and Paykel Healthcare Limited, New Zealand), applied continuously through large-bore binasal prongs, with a gas flow rate of 2 L/kg/min for the children less than equal to 10 kg and for children >10 kg 2 L/kg/min for the first 10 kg + 0.5 L/kg/min for each kg above that and FiO_2 of 0.4 at initiation.[11] The fraction of oxygen in the gas flowing in the system was subsequently adjusted to maintain a SpO_2 of 94% or more.

Primary endpoint assessments were done at 2, 6, 12, 24, 36, and 48 h after initiation of treatment. At 48 h, number of infants still maintaining stable parameters in both groups was noted. Medical treatment of infants with acute bronchiolitis remained unchanged for study purposes, as per the standard hospital protocol. A nasogastric tube was placed for enteral feeding.

In case of NIV failure, the protocol was stopped and clinical treatment was performed according to clinical judgment. Criteria for endotracheal intubation included (i) NIV failure; (ii) clinical signs of exhaustion; (iii) need to protect airways and/or manage copious tracheal secretions; (iv) persistent air leak; (v) deterioration in gas exchange, i.e., required FiO_2 >60% and SpO_2 <92%; (vi) patient intolerance; (vii) hemodynamic impairment; or (vii) major adverse patient event (hemodynamic instability, pneumothorax, hypercapnic coma, and cardiac arrest).

Statistical analysis

Outcome measure(s)

Primary outcome: Reduction of the need of MV, which was assessed by improvement in (i) HR; RR; (ii) RDAI from preintervention value; (iii) SpO_2 (iii) $PaCO_2$; (iv) partial pressure of oxygen (PaO_2); and (v) COMFORT Score.[12]

Secondary outcome: (i) Total duration of NIV support; (ii) PICU length of stay (LOS); and (iii) incidence of nasal injury (NI).

Definition(s)

"NIV failure:" If HR and/or RR remained unchanged/increased; required FiO_2 >60% for nCPAP with PEEP >8; required FiO_2 >60% for HHHFNC with maximum O_2 flow rate to maintain SpO_2 >94% and no improvement or increase in RDAI score.

The persistent air leak was defined as the presence of leaks around the interface that affected circuit pressurization <3 cm H_2O despite repeated positioning.

Tolerance to the interface was assessed by use of COMFORT scale, used by Bueno Campaña, *et al*.[12] According to this scale, maximum score was 16 which indicate maximum comfort state and the minimum score was 4 which indicate minimum comfort state.

Subjective assessment of respiratory distress was done according to RDAI[9] scoring based on wheezing/crackles and retractions (maximum point for wheezing = 8; retractions = 9) on both NIV types.

The nasal injuries were defined as the appearance of erythema with erosion, crusting and excoriation to scaling at the base of the septum, medial aspect of the septum, over the alae nasi and nasal bridge.

Statistical analysis

The GraphPad package (2015 GraphPad Software, Inc., CA, USA) was used for all analyses. Descriptive statistics was calculated for quantitative variables (mean ± standard deviation and 95% confidence interval, median with interquartile range) and for qualitative variables (absolute and percentage frequencies). Normality distribution was estimated by Kolmogorov–Smirnov test. Data showed mixed distribution. Continuous data were analyzed by Student's independent *t*-test (for parametric data) or Mann–Whitney U-test (for nonparametric data). Categorical data were analyzed by Chi-square or Fischer's exact test. $P < 0.05$ was considered statistically significant. Intention-to-treat analysis was used in this study, taking the worst case scenario for patients who dropped out from the study into consideration.

Sample size calculation

Calculations were based on data from data from previous studies.[3-6] Assuming risk of acute respiratory failure in nCPAP group at 40% and 20% in HHHFNC group, and considering α *error at* 5% and β at 20% the calculated sample size was 170. However, as the current study is a pilot study to assess the feasibility and obtain preliminary data, with the standardized effect size of 0.4, 80% power of the main study and 5% Type I error rate optimal pilot trial sample size calculated as 28. Anticipating a 10%–15% dropout rate; 31 patients were taken.

Results

The flow chart of study progress has been reported in Figure 1. From September 2016 to February 2017, 62 patients were admitted with the clinical diagnosis of bronchiolitis in our

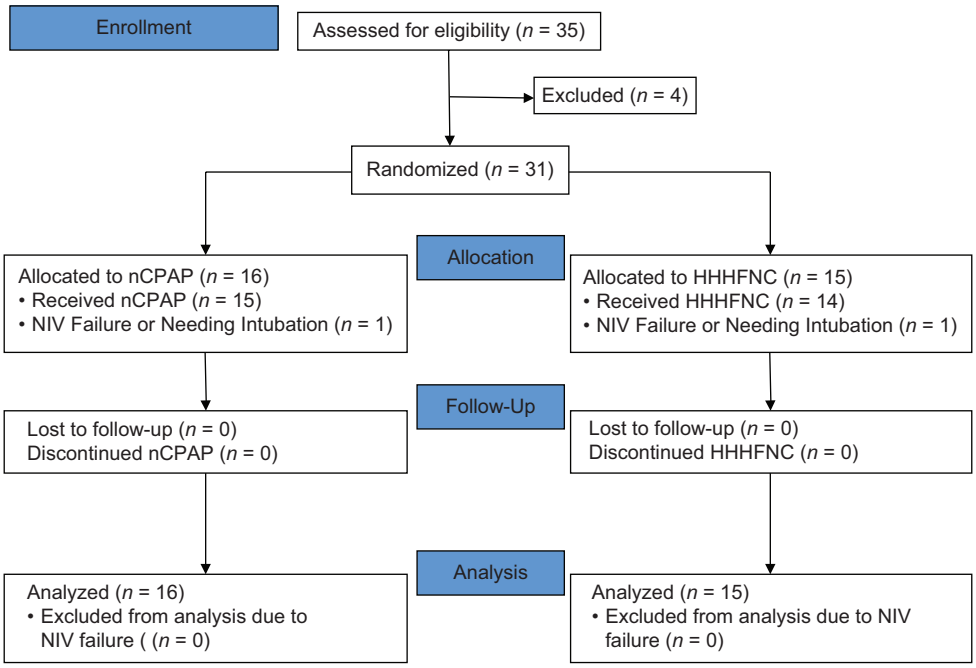

Figure 1: Adapted CONSORT flow diagram showing progression of patients through the trial

hospital. Thirty-five patients met the inclusion criteria. A total of 31 patients were randomized, 16 were allocated in nCPAP group and 15 in HHHFNC Group. Two patients were excluded for the need of immediate intubation, and two patients were excluded for hemodynamic instability. Mean age was 3.41 ± 1.11 months. There were no differences in baseline respiratory support parameters between groups [Table 1].

One patient in each group had NIV failure and had to be intubated; hence, intubation rates were similar in both groups ($P = 0.29$). Functional and subjective respiratory parameters such as SpO_2, RR, PaO_2, PCO_2, and RDAI scores compared between the two groups [Table 2]: All the parameters were improved steadily in both groups. Improvements in all end-points tested were comparable for both groups [Figure 2]. Compared to nCPAP, HHHFNC was better tolerated as indicated by better normalization of HR ($P < 0.001$); better COMFORT Score ($P < 0.003$).

Secondary outcome – Incidence of nasal injury was higher ($P = 0.021$) in nCPAP ($n = 12$, 75%) as compared to HHHFNC ($n = 4$, 26.66%). Mean duration of NIV on nCPAP (3.8 ± 0.80 days) and HHHFNC (3.6 ± 0.63 days) were comparable ($P = 0.33$). Average PICU LOS on nCPAP (5 ± 1.788 days) and HHHFNC (5 ± 1.6 days) were also comparable ($P = 0.105$).

Safety and adverse events

No major adverse events occurred during the study (cardiac arrest, pneumothorax, or safety system failures). Air leaks and skin sores were all more frequent in the nCPAP group ($P = 0.23$, 0.16, respectively). No significant differences were found between groups with respect to the incidence of gastric distension, eye irritation, and mortality.

Table 1: Baseline characteristics of study participants ($n=31$)

Variable	nCPAP group ($n=16$)	HHHFNC group ($n=15$)	P^a
Age (month)	2.81 (1.03)	4.06 (2.92)	0.66
Male:Female	10:6	4:11	
Unimmunized status, *n* (%)	3 (18.75)	2 (13.33)	
RR (breaths/min)	72.80 (3.78)	73.6 (3.55)	0.54
HR, (beat/min)	168.5 (5.72)	164 (8.75)	0.10
SpO_2 (%)	88.75 (1.43)	88.27 (2.46)	0.51
PaO_2	73.4±6.51	72.8±5.76	0.78
$PaCO_2$	42.5 (3.68)	44.27 (3.99)	0.11
Arterial pH	7.38 (0.45)	7.37 (0.5)	0.75
Body temperature (°C)	37.1 (0.6)	36.9 (0.5)	0.93
Comfort index	6.25 (0.44)	6.93 (0.59)	0.41
Mean blood pressure (mmHg)	55.6 (3.6)	56.3 (2.4)	0.53
RDAI	12.25 (1.0)	11.47 (1.68)	0.13

[a]Student independent *t*-test and Mann-Whitney U-test. Data expressed as *n* (%) or mean±SD. SD: Standard deviation; RR: Respiratory rate; HR: Heart rate; nCPAP: NoninvasiveCPAP; HHHFNC: Hot humidified high-flow nasal cannulae; RDAI: Respiratory Distress Assessment Index; CPAP: Continuous positive airway pressure

Discussion

In this study, we investigated the effects of HHHFNC compared to NIV therapy in patients with moderately severe bronchiolitis. We also conducted a subjective patient evaluation of the two oxygen applications. Our data suggest that HHHFNC and NIV are both equally effective to reduce the need of endotracheal intubation. Both groups were comparable in terms of duration of the need of support length of PICU stay.

Metge *et al*.,[13] in a retrospective study compared the use of a nasal continuous positive airway pressure (nCPAP) to an

Table 2: Primary outcome (s)

Parameters	T0	T2	T6	T12	T24	T36	T48
SpO_2 (%)							
HHHFNC	88.2±2.46	94.5±0.99	94.5±1.84	94.4±5.27	95.4±1.55	95.8±2.40	97.4±1.22
CPAP	88.7±1.43	94.1±1.62	94.3±2.06	95.6±1.78	95.3±1.62	95.3±1.66	97.0±1.36
RR (beats/min)							
HHHFNC	73.6±6.55	64.8±3.84	57.2±5.49	49.6±5.13	44.5±5.04	39.4±4.66	36.5±5.17
CPAP	72.2±3.78	66.0±4.84	58.3±4.31	48.7±3.08	47.8±3.94	42.7±2.29	36.2±2.40
HR (beats/min)							
HHHFNC	164.0±8.75	149.7±3.69	141.8±4.30	132.4±11.78	126.2±6.12	118.5±5.62	113.1±3.82
CPAP	168.5±5.72	160.1±5.27	150.8±3.98	146±4.61	138.3±4.12	129.8±2.65	123.7±3.92
PaO_2 (mmHg)							
HHHFNC	72.8±5.76	85.3±4.28	93.2±3.75	94.2±7.03	102.0±5.93	100±7.44	94.8±5.14
CPAP	73.4±6.51	83.3±4.82	92.9±4.25	91.2±10.64	98.0±5.73	99.7±5.70	98.4±6.74
$PaCO_2$ (mmHg)							
HHHFNC	44.2±3.99	44.4±3.99	47.3±3.92	47.3±7.84	39.1±4.94	37.1±3.48	40.0±4.40
CPAP	42.5±3.68	47.6±6.71	52±3.14	48.7±4.75	45.1±2.65	41.7±4.91	37.2±4.09
RDAI							
HHHFNC	11.4±1.68	8.6±0.98	8.0±1.25	7.2±2.08	5.2±1.63	3.1±0.86	2.1±0.86
CPAP	12.2±1.00	9.0±1.03	9.0±1.03	6.7±1.00	5.6±0.88	3.3±0.50	2.2±0.68
Comfort index							
HHHFNC	6.9±0.59	8.7±0.45	9.4±0.91	10.8±1.56	12±0.00	13.1±1.02	14.5±0.51
CPAP	6.2±0.44	6.8±0.61	8.2±0.85	9.0±0.51	9.8±0.80	11.1±0.80	12.2±1.00

Data expressed as mean±SD. SD: Standard deviation; RR: Respiratory rate; HR: Heart rate; CPAP: Noninvasive CPAP; HHHFNC: Hot humidified high-flow nasal cannulae; RDAI: Respiratory Distress Assessment Index; CPAP: Continuous positive airway pressure

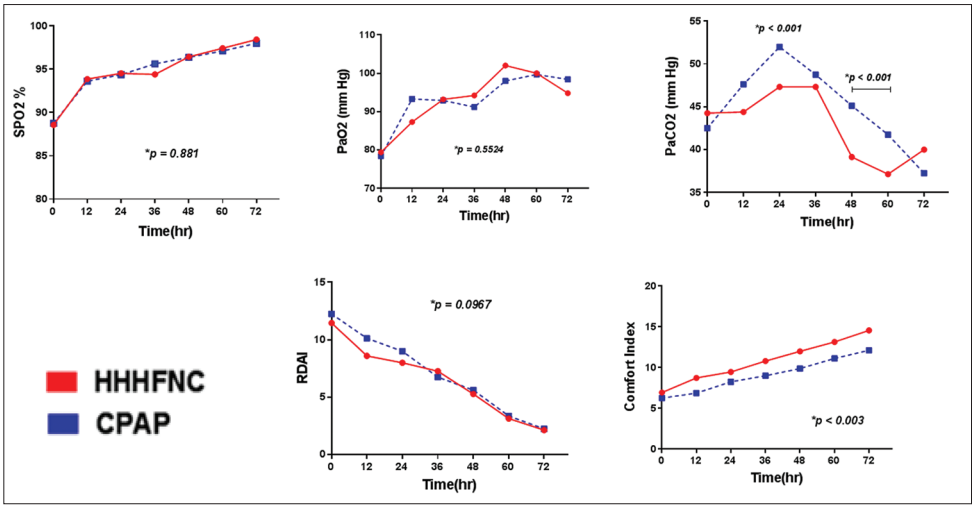

Figure 2: Primary outcome measures; plot showing difference between two groups

HFNC in infants with acute Bronchiolitis. Parameters such as LOS in PICU and oxygenation were similar in the two groups. Oxygen weaning occurred during the same time for the two groups. There were no differences between the two groups for RR, HR, FiO_2, and CO_2 evolution. HFNC therapy failed in three patients, two of whom required invasive MV, versus one in the nCPAP group. These results are in concordance to our findings.

On the contrary Pedersen *et al*.[14] in a recent (2017) study from Denmark showed CPAP was superior to HFNC in lowering RR and FiO_2 in infants with bronchiolitis. More than half of the children treated with HFNC were changed to CPAP treatment due to suspected treatment failure. There were no differences between HFNC and CPAP in treatment length, hospitalization length or transfer to PICU. However, the study was limited by its retrospective, unrandomized design, and the lack of standardized measurements. It could be planned in a prospective design (e.g., a standardized clinical score and control pCO_2).

There is lack of robust data comparing both therapies, though individually, both have been studied in different setups. An RCT comparing placebo versus nCPAP therapy in

children <3 years with acute bronchiolitis found that nCPAP significantly improved the RR. However, changes in SpO_2% and $PaCO_2$ data were imprecise, and duration of hospital stay was similar in both groups.[15] A study evaluating the feasibility of nCPAP for infants with Bronchiolitis in a pediatric ward, reported a decline in median $PaCO_2$ after therapy, thus it was concluded that nCPAP may be feasible in such setting, provided sufficient trained staffs and PICU referral setups were available.[16] Another study reviewing the use of nCPAP (either alone or associated with Heliox) reported a reduction of PaCO2, RR, and the modified Woods clinical asthma score after 1 h of treatment. However, after applying the GRADE system, the quality of evidence for a beneficial effect of nCPAP was considered as low.[17]

In a Cochrane review article including RCTs or quasi-RCTs which assessed the effects of HHHFNC to conventional treatment in infants with a clinical diagnosis of bronchiolitis, concluded that there is insufficient evidence to determine the effectiveness of HHHFNC therapy for treating infants with bronchiolitis. Previous two clinical studies, which used HHHFNC therapy in a nonrandomized manner showed a reduction in intubation rates in critically ill infants in PICU.[18,19]

This was a pilot study to assess feasibility and obtain primary data. It was limited by small sample size and single-center study. Large multiple center RCT is required to obtain robust data to compare effectiveness of these two methods of respiratory support in acute severe bronchiolitis.

Conclusion

Our results suggest that patients on HHHFNC were more comfortable than on nCPAP. Greater improvement in breathing pattern, better normalization of physiologic parameters (viz., HR and COMFORT index) and lower incidence of adverse events (nasal injury, air leaks, and skin lesions) makes HHHFNC a more feasible alternative in infants. Such results merit further exploration in a larger cohort.

Acknowledgments

We would like to thank the faculty of Department of Pediatrics & all the staffs of PICU, Medical College Kolkata, for assisting us in carrying out this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. Am J Respir Crit Care Med 2003;168:1277-92.
2. Oakley E, Borland M, Neutze J, Acworth J, Krieser D, Dalziel S, *et al.* Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: A randomised trial. Lancet Respir Med 2013;1:113-20.
3. Essouri S, Chevret L, Durand P, Haas V, Fauroux B, Devictor D, *et al.* Noninvasive positive pressure ventilation: Five years of experience in a Pediatric Intensive Care Unit. Pediatr Crit Care Med 2006;7:329-34.
4. Javouhey E, Barats A, Richard N, Stamm D, Floret D. Non-invasive ventilation as primary ventilatory support for infants with severe bronchiolitis. Intensive Care Med 2008;34:1608-14.
5. Lazner MR, Basu AP, Klonin H. Non-invasive ventilation for severe bronchiolitis: Analysis and evidence. Pediatr Pulmonol 2012;47:909-16.
6. Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: A critical review of the literature. Intensive Care Med 2013;39:247-57.
7. Wiswell TE, Courtney SE. Noninvasive respiratory support. In: Goldsmith JP, Karotkin EH, editors. Assisted Ventilation of the Neonate. 5th ed. St. Louis: Elsevier Saunders; 2011. p. 140.
8. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: Mechanisms of action. Respir Med 2009;103:1400-5.
9. Corneli HM, Zorc JJ, Holubkov R, Bregstein JS, Brown KM, Mahajan P, *et al.* Bronchiolitis: Clinical characteristics associated with hospitalization and length of stay. Pediatr Emerg Care 2012;28:99-103.
10. Stephen MS, Elizabeth AS, Michael HS, Michele MM, Ashley SR, Richard TF, *et al*. Pediatric vascular access and centeses. In: Fuhrman BP, Zimmerman JJ, editors. Pediatric Critical Care. 4th ed. Philadelphia: Elsevier; 2011. p. 139-63.
11. Royal Children's Hospital, Melbourne, Australia, Clinical Practice Guideline on High Flow Nasal Prong HFNP Oxygen. Available from: http://www.rch.org.au/clinicalguide/index.cfm. [Last updated on 2013 Jul 24; last accessed on 2018 Jan 01].
12. Bueno Campaña M, Olivares Ortiz J, Notario Muñoz C, Rupérez Lucas M, Fernández Rincón A, Patiño Hernández O, *et al.* High flow therapy versus hypertonic saline in bronchiolitis: Randomised controlled trial. Arch Dis Child 2014;99:511-5.
13. Metge P, Grimaldi C, Hassid S, Thomachot L, Loundou A, Martin C, *et al.* Comparison of a high-flow humidified nasal cannula to nasal continuous positive airway pressure in children with acute bronchiolitis: Experience in a Pediatric Intensive Care Unit. Eur J Pediatr 2014;173:953-8.
14. Pedersen MB, Vahlkvist S. Comparison of CPAP and HFNC in management of bronchiolitis in infants and young children. Children (Basel) 2017;4. pii: E28.
15. Jat KR, Mathew JL. Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. Cochrane database of systematic reviews 2015. CD010473.
16. Oymar K, Bårdsen K. Continuous positive airway pressure for bronchiolitis in a general paediatric ward; a feasibility study. BMC Pediatr 2014;14:122.
17. Keenan SP, Sinuff T, Cook DJ, Hill NS. Does noninvasive positive pressure ventilation improve outcome in acute hypoxemic respiratory failure? A systematic review. Crit Care Med 2004;32:2516-23.
18. Schibler A, Pham TM, Dunster KR, Foster K, Barlow A, Gibbons K, *et al.* Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med 2011;37:847-52.
19. Ten Brink F, Duke T, Evans J. High-flow nasal prong oxygen therapy or nasopharyngeal continuous positive airway pressure for children with moderate-to-severe respiratory distress?. Pediatr Crit Care Med 2013;14:e326-31.