Title. Impact of different nebulization systems on patient comfort in bronchiolitis: a randomized controlled crossover trial

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ABSTRACT

Objective. To test the hypothesis that greater comfort is achieved using a nebulizer integrated into a high-flow nasal cannula (NHF) than using a jet nebulizer (JN), and to explore differences in analgesia requirement and the possibility of feeding during nebulization.

Design. Randomized crossover trial

Setting. Pediatric intensive care unit

Patients. Children aged <24 months diagnosed with bronchiolitis between November 2016 and May 2017

Interventions. Nebulizations using NHF and JN

Main outcome measures. COMFORT-B scale (CBS) and Numeric Rating Comfort Scale (NRSc) were used to measure comfort, and Numeric rating Satisfaction scale (NRSs) was used to assess satisfaction before, during, and after nebulization. Other variables included feeding, analgesia, need for being held, and respiratory and heart rates.

Results. Thirty-three children with 233 nebulizations were included in the study. The median (interquartile range) age was 3.0 (2;9) months. Comfort and satisfaction were greater with NHF than with JN. The median staff-recorded CBS, NRSc, and NRSs scores for NHF vs. JN were 13 (9;15) vs. 17 (13;23), 8 (7;10) vs. 7 (4;8), and 4 (3;4) vs. 2 (2;3), respectively; and caregiver-recorded scores were 12 (10;15) vs. 19 (13;24), 9 (7;10) vs. 4 (1;6), and 4 (3; 4) vs. 2 (1;3), respectively (P<.001). Children who received NHF had lower cardiac and respiratory rates, needed to be held less often during therapy, and required less analgesia (P <.001).

Conclusions. Nebulization through NHF appears to be a better alternative to JN in terms of comfort and satisfaction as well as making feeding possible during nebulization.

What is already known on this topic?

- The guidelines discourage the use of aerosol therapy owing to their lack of efficacy, poor tolerability, and the discomfort caused by jet-type nebulizers.
- The use of a high-flow nasal cannula (HFNC) has become widespread and seems to be a safe and effective respiratory support system in children with bronchiolitis.
- With the addition of HFNC to the treatment of these infants, a window of opportunity has been opened for nebulization through this system.

What this study adds?

- Nebulization through HFNC appears to be a better alternative to JN in terms of comfort and satisfaction, as measured by staff and caregivers using validated clinical scales.
- Nebulization through HFNC reduces analgesic requirements and makes feeding during nebulization more feasible.
- These findings could serve as a gateway for further research on the efficacy of nebulization in bronchiolitis, which might help improve future management and outcomes.

INTRODUCTION

Although bronchiolitis is the most common cause of hospital admissions during infancy, its clinical management is heterogeneous and continues to be revised every year.[1] Current guidelines discourage the use of aerosol therapy because of its low efficacy, poor tolerability, and the discomfort caused by jet-type nebulizers, especially in younger infants.[2] While a definitive specific treatment is long awaited, the mainstay of current recommendations focuses on ensuring adequate nutrition and respiratory support while maximizing patient's comfort during nebulization.

Because of its simplicity, good tolerability, and safety, as well as the good results reported in clinical studies, the high-flow nasal cannula (HFNC) is increasingly becoming popular and is now widely used in infants with bronchiolitis. [3-5] Addition of HFNC to the treatment of these infants has opened a window of opportunity for nebulization using this system. A recent study that used clinical scales to evaluate six patients with bronchiolitis showed that the patients had a greater comfort and satisfaction using a nebulizer integrated into HFNC (NHF) than while using the conventional nebulizer.[6] A study involving a larger sample size, inclusion of cutoff points strengthening the validity of scales,[7] and analysis of certain key variables, such as the use of analgesia and the possibility for feeding, for these patients,[8, 9] would strengthen these promising results and offer guidelines on their clinical application.

We performed a randomized crossover trial, in critically ill infants with bronchiolitis, with the following two aims: 1) to test the hypothesis that greater comfort is achieved during therapy using an NHF than with a jet nebulizer (JN), and 2) to explore the differences between the two nebulization systems in terms of the ability to feed during nebulization and analgesia requirements.

METHODS

Trial design

This was a randomized crossover trial conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. It was carried out in the pediatric intensive care unit (PICU) of a tertiary hospital, and it included children who were younger than 24 months of age, diagnosed with bronchiolitis, and received HFNC as respiratory support treatment between November 2016 and May 2017. Patients whose caregivers did not provide informed consent and those who had contraindications for HFNC (upper airway abnormalities that may make HFNC ineffective or potentially dangerous, life-threatening hypoxia, hemodynamic instability, facial bone or skull base trauma, and pneumothorax) were excluded.

Acute bronchiolitis was diagnosed according to the definition provided by the National Institute for Health and Care Excellence (NICE). Each patient's bronchiolitis scale score (0-5 = mild; 6-10 = moderate, and 11-16 = severe) was recorded at admission.[10]

Randomization

To ensure allocation concealment, the participants were randomly selected, using computer-generated random numbers, to begin nebulization with either JN or NHF. The nebulization device was then alternated in subsequent medication doses. Owing to the non-pharmacological nature of the interventions, only the outcome assessors and data analysts (not the participants or health staff) were blinded to the group allocation.

The number of nebulizations and choice of drug (salbutamol, 3% hypertonic saline, or epinephrine) for each subject depended on the clinician's decisions. The HFNC was delivered using an Optiflow system (Fisher & Paykel, Auckland, New Zealand).

JN group: The HFNC was not removed, and the flow rate was not modified when positioning the jet nebulizer face mask. As a standard, the Cirrus 2 Pediatric mask (Intersurgical, Wokingham, United Kingdom) was connected to a JN at a gas flow rate of 8 L/min (Supplementary figure).

NHF group: The nebulizer integrated into the HFNC system consisted of a mesh nebulizer (AeroNeb Solo, Aerogen, Galway, Ireland) connected to the dry side of an MR290 humidifier chamber (Fisher & Paykel) (Supplementary figure).

Comfort, satisfaction, and intercurrent variables analyzed

For each nebulization, comfort and satisfaction were recorded 5 min before, 5 min during, and 5 min after treatment by both the PICU staff (mainly nurses) and caregivers.

Comfort was assessed using the COMFORT-Behavior scale (CBS) and a variant of the Numeric rating comfort scale (NRSc). [11, 12] In the CBS, the score 30 represents no comfort and 6 represents the best comfort imaginable. In the NRSc, 0 represents no comfort and 10 represents the best comfort imaginable. CBS scores from 17 to 30 and NRSc score of 6 or lower suggest pain and need for intervention, according to the appropriate pain and sedation protocols. [13, 14] Satisfaction was defined as the feeling of well-being or pleasure that the patient had with the intervention and was recorded by the healthcare team and caregivers through a numeric rating satisfaction scale (NRSs), where 0 indicates no satisfaction and 4 indicates the best satisfaction imaginable.

Heart rate (HR), respiratory rate (RR), and surrogate variables of discomfort, such as the possibility to be fed, analgesia requirements, and the need to be held in the caregivers' arms, were also recorded. (Supplementary figure).

Analysis

Qualitative variables were summarized as absolute and relative frequencies and quantitative variables as median (with interquartile range [IQR)]) or mean (with standard deviation). Continuous variables were compared using the Mann–Whitney U test or Kruskal–Wallis test when appropriate. Categorical variables were compared using the chi-squared or Fisher's exact test. Spearman's coefficient (rs) was used to measure correlations between the different measuring scales. Repeated-measures analysis of variance (ANOVA), adjusted for the type of nebulization system and the patient identification number, was performed to determine the existence of

differences among the three periods of comfort assessment (before, during, and after nebulization).

Statistical significance was set at P <0.05. For multiple comparisons and repetition of comparisons, Bonferroni adjustment was applied, and the corrected level of significance was p-value <0.025. Statistical analyses were performed using the software Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS, Armonk, NY, USA). The number of nebulizations to be recruited to achieve a power of 0.9, alpha error of 0.05, and mean difference of 3 points in the comfort scale (standard deviation of 6.5 points) was 101 nebulizations in each group. This value was based on the results of our previous pilot study.[6]

Ethics statement

The study was registered in our institutional clinical trial database and was approved by the Clinical Research Ethics Committee (ID 1558). Written informed consent was obtained from the caregivers.

RESULTS

Overall, 233 nebulizations were administered to 33 patients with acute bronchiolitis. The median age of the patients was 92 days (IQR, 53; 208 days). For 25 (76%) children, it was their first episode of bronchiolitis, and the median severity score was 8 (IQR 7; 10). The most frequently involved microorganism was the respiratory syncytial virus in 27 children (82%).

Of the 233 nebulizations, 109 were delivered via JN and 124 via NHF (Figure 1). No differences were found between the drugs used in the two systems (salbutamol, 3% hypertonic saline, or epinephrine) ($p = 0.906$).

Comfort and satisfaction assessment for each nebulization system

We found a strong negative correlation between the CBS and NRSc scales (rs = −0.74, $p < 0.001$ assessed by the healthcare team and rs = −0.83, $p < 0.001$ by caregivers).

The CBS and NRS scores measured by the healthcare team and caregivers were statistically significant showing greater discomfort during nebulization with the JN system than with the NHF (Table 1 and Figure 2).

Regarding discomfort, more infants achieved a CBS score ≥17 or NRSc ≤6 during nebulization using JN than using NHF, as assessed by the healthcare team. When nebulizations were administered using the NHF system, only 8% and 17% of the interventions changed to a CBS score ≥17 or NRSc ≤6, respectively; whereas the corresponding values were 38% and 45% for the interventions with the JN system ($p < 0.001$).

Furthermore, both cutoff points were reached (CBS ≥17 and NRSc ≤6) significantly more frequently with JN than with NHF [64% vs. 17% and 44% vs. 10%, respectively ($p < 0.001$)], as reported by both caregivers and staff.

Compared to the healthcare team, the caregivers recorded greater discomfort when the JN system was used. The CBS score increased by 30% when the JN nebulization was implemented compared to 23% as assessed by the healthcare team ($p = 0.46$), and NRS decreased by 33% as assessed by caregivers compared to 27% recorded by the healthcare team ($p = 0.012$).

Patient satisfaction perceived by caregivers and the healthcare team measured with NRSs was higher with the NHF system than with the JN system ($p < 0.001$) (Table 1).

Physiological variables, feeding possibility, and need for analgesia

The correlation between the CBS score and HR was moderate (rs = 0.595 [p <0.001]), whereas it was low with RR (rs = 0.234 [p <0.001]). The HR increased by 10% with CBS scores ≥17 compared to 1.7% when the CBS score was <17 (p <0.001). HR increased significantly during nebulization in both systems, but this increment was greater with JN than with the NHF (7% vs. 2%, respectively) (p <0.001) (Table 2).

Feeding was undertaken during nebulization in 27 episodes with NHF (21 orally and 6 via nasogastric tube) and 3 nebulization episodes with JN (all via nasogastric tube) (p <0.05).

Analgesia (paracetamol and/or sucrose) was used during nebulization in 5% of the episodes with JN and 2% with NHF, and there was a significant difference in the need for analgesia after nebulization (6% with JN and 1% with NHF, p = 0.028) (Table 2). These differences were not related to the drugs used.

The need for children to be held in caregivers' arms rose by 48% during nebulization using JN but remained the same with NHF (p <0.05).

DISCUSSION

Based on this randomized crossover trial in infants with bronchiolitis, we confirmed that NHF nebulization is more comfortable than the traditional JN system, as assessed by both healthcare professionals and caregivers using validated clinical scales. This is also supported by the observed variations in physiological values (such as HR and RR), feeding possibility, and the need for analgesia.

Although no clear benefit has been found so far to support the use of nebulizations in bronchiolitis, [15, 16] it has been previously reported that one of the factors that can modify the efficacy of a nebulized drug is the patient's ability to tolerate the nebulizer.[17] Thus, it seems relevant to explore the possibility of using the HFNC support, which is becoming widely available, in these children to carry out nebulizations in a more comfortable way than in JN.

In this study, we used the CBS and NRS clinical scales, which are validated tools for assessing comfort, in patients hospitalized in the PICU. [13, 14] We found a good correlation between the two clinical scales, whether applied by staff or caregivers, which lends support to their utility in clinical practice. We confirmed, using a larger sample than that in a previous pilot study by our group, that the NHF system is more comfortable than the JN system. In addition, the staff reported that the infants developed pain in 38% (CBS ≥17) or 45% (NRSc ≤6) of the nebulization episodes using the JN system, which was previously below the cutoff points. In the case of the NHC system, this only occurred in 8% (CBS ≥17) or 17% (NRSc ≤6) of the interventions.

Parent involvement in the care of PICU children is one of the mainstays of family-centered care of critically ill pediatric patients. [18, 20] An interesting aspect of our study is that the caregivers reported worse discomfort with the JN system than the health care staff did. Further, the consistency between the two groups highlights the validity of the scales and the positive impact of the presence of parents in the PICU.[20]

Caregivers of children hospitalized for severe bronchiolitis exhibit remarkably high levels of anxiety during their child's hospitalization, and the feeding process is one cause of this stress .[21] Moreover, oral feeding is generally recommended as a first-line nutritional strategy, especially in cases of bronchiolitis in breast-feeding infants, and the infants with bronchiolitis being treated with HFNC can be safely fed via enteral route.[22, 23] In this study, the feeding factor, in addition to the reduced analgesia requirement, might have played key roles in the improved comfort and satisfaction perceived with the NHF system.

Analgesia is a fundamental component in the treatment of these patients because it allows the nursing staff to perform invasive procedures safely.[8] Although painful and stressful procedures are, unfortunately, not completely avoidable in pediatric critical care,[24] our results show that reducing discomfort during nebulization, and in turn decreasing analgesic intervention, is possible. This could help minimize unwanted effects, such as decreased immune response, poor sleep, decreased physical function, anxiety, and future psychiatric problems, associated with poorly controlled pain.[25]

Furthermore, physiological variables such as cardiac and respiratory rates, which are fundamental factors in the bronchiolitis severity scales and assessment of treatment success in patients with respiratory failure,[10] were significantly increased during nebulization with the conventional system. This seems to support the conclusion, previously obtained from the clinical scales, that there is a difference in the level of comfort experienced with each nebulization system. Furthermore, it lends support to the use of these variables in further studies to assess the efficacy of nebulized drugs in this illness.

This study has some limitations. It was performed at a single center. Besides, comfort and satisfaction were measured by caregivers and personal staff who were clearly able to see which treatment was being employed; thus, inherently imparting bias. Additionally, other variables which could influence stress and discomfort, such as noise and brightness levels, were not recorded. [26] It would have been of interest to record body temperature, since its variation can affect HR. Another challenge is that most comfort scales include HR among the variables to be scored; therefore, it would be very difficult to differentiate changes in HR induced by pain or discomfort from the changes induced by the nebulized drugs. In this study, however, we believe that this was not a real limitation because the drugs employed were arbitrarily chosen, and the nebulization were randomly administered using one of the two nebulizers. Finally, future studies should address optimal flow in terms of adequate drug delivery rates.

CONCLUSION

Reducing patients' discomfort is an ethical imperative, and the efficacy of treatments causing such discomfort is not clear. Clinical scales, including the analysis of cutoff points, are suitable and necessary for assessing the degree of comfort or pain experienced by pediatric in-patients during procedures. A nebulization system integrated into a high-flow oxygen therapy interface allows for a greater level of comfort than the conventional system currently used in the treatment of bronchiolitis. It also achieves better satisfaction scores with healthcare providers and even more with caregivers. In addition, the reduced analgesic requirements and the greater possibility for feeding during nebulization with the NHF system represent a gateway for further research on the

efficacy of nebulization in bronchiolitis. This may also help improve future management and outcomes.

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The authors declare no conflicts of interest.

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FIGURE LEGENDS

Figure 1.

Flow chart of the study enrolling children aged <24 months, hospitalized for an acute viral bronchiolitis, and treated with 2 different nebulizers (NHF = nebulizer integrated in high flow nasal cannulas; JN = jet nebulizer).

Figure 2.

Comfort-Behavior scale (CBS) and numeric rating comfort scale (NRSc) assessed by healthcare team and caregivers before, during, and after nebulization with the two systems.

TABLES

Table 1. Comfort and satisfaction analyzed by health staff and caregivers using the two nebulization systems.

	Total nebulizations *n* =233			JN nebulizations *n* =109			NHF nebulizations *n* =124		
	n	Median	IQR	n	Median	IQR	n	Median	IQR
Healthcare team									
Comfort-B									
Before NB	232	12	(8; 15)	109	13	(9; 16)	123	11*	(7; 14)
During NB	229	14**	(10; 19)	108	17**	(13; 23)	121	13*/**	(9; 15)
After NB	224	13**	(8; 15)	107	13**	(10; 15)	117	12**	(8; 15)
NRSc									
Before NB	229	9	(8; 10)	107	8	(7; 10)	122	9*	(8; 10)
During NB	226	8**	(6; 9)	105	7**	(4; 8)	121	8*/**	(7; 10)
After NB	222	9**	(7; 10)	105	8**	(7; 9)	117	9**	(7; 10)
NRSs during NB	231	2**	(2; 3)	108	2**	(2; 3)	123	4*/**	(3; 4)
Caregivers									
Comfort-B									
Before NB	102	12	(10; 15)	49	13	(10; 16)	53	12	(8; 14)
During NB	104	14**	(11; 21)	51	19**	(13; 24)	53	12*/**	(10; 15)
After NB	102	12**	(10; 15)	51	13**	(10; 16)	51	12	(9; 14)
NRSc									
Before NB	78	8	(7; 10)	37	8	(5; 9)	41	9*	(8; 10)
During NB	78	7**	(3; 9)	37	4**	(1; 6)	41	9*	(7; 10)
After NB	77	8**	(6; 10)	37	7**	(5; 9)	40	9*	(7; 10)
NRSs during NB	91	3	(2; 4)	45	2	(1; 3)	46	4*	(3; 4)

NB, nebulization; NHF, nebulization system integrated in high-flow nasal cannula; JN, jet nebulizer; NRSc, numeric rating comfort scale; NRSs, numeric rating satisfaction scale.

* $p < 0.05$ when comparison was made between NHF and JN

** $p < 0.025$ was considered statistically significant after Bonferroni correction was made for comparisons between the following time points: NB vs before-NB, and after-NB vs NB

Table 2. Comparison of physiological, analgesic, and feeding variables between the two nebulization systems.

	JN nebulizations *n*=109	NHF nebulizations *n* =124
Heart rate (beats/min)		
Before nebulization	136 (124; 145)	132 (118; 145)
During nebulization	146 (134; 161) **	135 (119; 152) */**
After nebulization	138 (128; 152)	138 (121; 153)
Respiratory rate (/min)		
Before nebulization	29 (24; 35)	29 (23; 36)
During nebulization	31 (26; 38) **	33 (28; 40) **
After nebulization	30 (25; 35)	30 (25; 36)
Analgesia		
Before nebulization	6 (6)	1 (1)
During nebulization	5 (5)	2 (2)
After nebulization	7 (6)	1 (1) *
Held in arms		
Before nebulization	13 (12)	12 (10)
During nebulization	25 (23) **	13 (10) *
After nebulization	23 (21)	8 (7) *
Fed within 1 hour before starting nebulization	41 (43)	44 (44)
Feeding during nebulization	3 (3)	27 (22)
Orally	0	21
Nasogastric tube	3	6
Time of the day		
Day time (08:00h-22:00h)	86 (79)	84 (68)
Night time (22:00h-08:00)	23 (21)	40 (32)

NHF, nebulization system integrated in high-flow nasal cannula; JN, jet nebulizer.
Quantitative variables are expressed in median (P25–P75).
Categorical variables are expressed in *n* (%).
* $p < 0.05$ when comparison was made between NHF and JN
** $p < 0.025$ was considered statistically significant after Bonferroni correction was made for comparisons between the following moments: during nebulization vs before nebulization, and after nebulization vs during nebulization