Incorporating a nebulizer system into high-flow nasal cannula improves comfort in infants with bronchiolitis.

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INTRODUCTION: High-flow nasal cannula (HFNC) is increasingly used as respiratory support in infants with bronchiolitis. The delivery of aerosol therapy through jet nebulizer (JN) is widely indicated despite its controversial efficacy and poor tolerability.

METHODS: Cross-over randomized study to evaluate the comfort and satisfaction of the delivery of aerosol therapy using a nebulization system integrated into HFNC (NHF) compared with standard practice, a JN with a face mask. COMFORT-B scale (CBS), visual analogue scale (VAS) and numeric rating scale (NRS) were used to determine the level of comfort and satisfaction assessed by health professionals and caregivers.

RESULTS: A total of 113 nebulizations (64 NHF; 49 JN) were delivered to the 6 subjects included in the study. NHF showed increased comfort and satisfaction during nebulization compared to JN, measured by the CBS, VAS and NRS scales (medians; interquartile ranges): 10.7 (7;16) vs 14.5 (10;20), 8.5 (6;10) vs 7 (4;9) and 3.84 (3.61; 4.07) vs 1.83 (1.58; 2.08) respectively ($P < .05$). Correlation (Spearman´s rho) between CBS and VAS scale was -0.757 ($P < .001$). The intraclass correlation coefficient for CBS, VAS and NRS, measured by 2 different nurses was between 0.75 and 0.87.

CONCLUSIONS: The use of a nebulizer incorporated to HFNC results in an increased level of comfort and satisfaction compared to the use of a conventional jet nebulizer in patients with bronchiolitis who require HFNC therapy. Further studies are needed to find out whether aerosol therapy delivered through HFNC improves the clinical course of this pathology.

Key Words

High-flow oxygen therapy; Nebulization; Comfort; Bronchiolitis; Satisfaction; Jet nebulizer*;* Aerogen

INTRODUCTION

Bronchiolitis is an acute inflammatory injury of the bronchioles caused by a viral infection in infants[1]. It has an annual incidence of 7% to 20%, and a hospitalization rate of between 3% and 5% [2, 3], with a mean hospital stay of 1.2 to 8 days [4]. This high use of medical care translates into a significant social and economic impact [5, 6].

Aerosol therapy in this disease is continually re-evaluated. Nebulization with salbutamol, epinephrine or 3% hypertonic saline are used in clinical practice, with the aim of performing initial efficacy tests or attempting to improve clinical severity[7-11]. These drugs are generally administered with a jet nebulizer (JN) connected to a face mask, despite its poor tolerability and insufficient particle deposition in the lungs in many cases [12, 13]. Cooperation during administration remains the most important factor for drug delivery [14], and particularly in neonates and small children, in which the nasal route for aerosol delivery to the lower respiratory tract is more efficient than mouth breathing[15-17].

The efficacy and safety of High-flow oxygen therapy (HFNC) has made it one of the most used respiratory supports in infants with bronchiolitis [18]. Nevertheless, the use of JN in patients receiving HFNC requires the discontinuation of respiratory support to release the nasal route, as well as frequent awakening which often results in increased irritability of the patient. Thus, a system to deliver both oxygen and medication without patient manipulation, would prevent discomfort and favorably affect the course of the disease. This possibility has been scarcely studied in vitro [19-21] and in one descriptive clinical study [22].

Our aim was to evaluate in a cross-over randomized study the comfort and satisfaction of the delivery of aerosol therapy using a nebulization system integrated into HFNC (NHF) compared with standard practice, a jet nebulizer with a face mask (JN). Comfort and satisfaction were examined through different validated medical scales and assessed by health personnel and caregivers in children with bronchiolitis.

METHODS

This is a prospective randomized and cross-over study that included 6 children less than 24 months-old with bronchiolitis who received respiratory support with HFNC (March 2016). Two hospitals participated in the study, a secondary level hospital where standard low-flow therapy or HFNC was used as respiratory support, and the pediatric intensive care unit of a tertiary hospital where HFNC was administered after initial stabilization with non-invasive ventilation or artificial ventilation, depending on the severity of the bronchiolitis.

Bronchiolitis was defined as a clinical syndrome that occurred in children <2 years of age characterized by upper respiratory symptoms followed by signs of lower respiratory infection with inflammation, resulting in wheezing and/or crackles. Bronchiolitis Scale (San Juan de Dios Hospital-Bronchiolitis Scale [23] (0-5points=mild, 6-10=moderate, 11-16=severe) was registered at admission. The study was approved by the Clinical Research Ethics Committee (1558). Informed consent was requested from parents.

Respiratory support and aerosol therapy

After parental consent was obtained, subjects were randomized by a computer-generated random number list to begin the nebulization with a jet nebulizer (JN) or NHF, alternating the nebulization device in subsequent medication doses. Support with HFNC was not removed when placing the JN facemask. The number of nebulizations and the choice of drug (salbutamol, 3% hypertonic saline or epinephrine) in each subject depended on the subject's clinical situation and medical criteria.

The OptiflowTM system (MR850 humidifier with an RT329 infant heated circuit) was used with neonatal sized nasal cannula (BC2435) with gas flow <8 L/min and infant cannula (BC2755) for >8 L/min, all by Fisher & Paykel Healthcare, Auckland, New Zealand.

The standard practice for JN consisted of a jet nebulizer connected to a face mask (Cirrus 2 Paediatric, Intersurgical, Wokingham, UK) with a gas flow of 8 L/min. In case of the nebulizer JN, the final flow rate was that of the JN and HFNC.

The NHF was a mesh nebulizer Aerogen Solo (AeroNeb Solo, Aerogen, Galway, Ireland) connected on the dry side of the MR290 humidifier chamber (Fig. 1).

Comfort analysis

Comfort and satisfaction were recorded for each nebulization at 3 different times (5 minutes before, during, and 5 minutes after the nebulization) by two nurses and the caregivers of the subjects (see Appendix 1 in the supplementary materials). Comfort was analyzed using the COMFORT Behavior Scale (CBS) [24] and a visual analog scale (VAS) [25]. The CBS is scored from 1 to 5 and the final score range is the sum of the six behavioral items, with a total score ranging from 6 to 30. All nurses underwent previous training through an accredited course, with the videos of the COMFORT-B scale provided by Monique van Dijk of the Erasmus MC-Sophia Children's Hospital. VAS represents a horizontal continuous 10-cm line with 'no comfort" on the left side and 'extreme comfort' on the right side. Satisfaction was measured with a numeric rate scale (NRS). NRS is a global pain rating scale which rates pain intensity by number (0=no pain and 4 = worst imaginable pain).

One month before starting the study, involved health personnel received a training course on the different scales that would be used, as well as the methodology and schedule to be followed.

Other variables analyzed

In each nebulization the following variables were recorded: Date and time; food intake; received analgesia; physiological variables (Heart Rate, Breathing frequency, Oxygen saturation and Fraction of inspired oxygen), HFNC parameters (air flow rate and temperature) (see Appendix 1 in the supplementary materials).

Data analysis and statistics:

Absolute and relative frequencies were calculated for each qualitative variable, and the differences based on nebulization system were identified using Chi-square or Fisher's exact test. For quantitative variables, median and interquartile range were obtained according to nebulization system and time period. Spearman's coefficient was used to measure correlation among the different measuring scales, and the intraclass correlation coefficient was used to evaluate the consistency of the scores obtained by nursing staff. Nonparametric testing (Mann-Whitney's U test) was used to compare both nebulization systems in each time period. Repeated measures ANOVA was performed in order to determine the existence of differences due to the nebulization system used in relation to each subject's comfort scores, severity scores and duration of hospital admission. Using repeated measures ANOVA it is

possible to adjust the analysis by patient, controlling the existing differences by treatment (which is the same in each patient). Given that each patient received both kinds of treatments in various occasions, carry-over effect and interaction by order of administration were not expected.

The number of paired measurements that should be recruited to estimate a paired mean difference of comfort scale of two points (difference standard deviation 4 points) with a power of 0.8 and an alfa error of 0.05 was 34. Power estimation for comfort scale was made with G*Power 3.1.9.2 [26]. We estimated that a sample size of 113 measurements has a post-hoc achieved power of 0.99 in repeated measures ANOVA (within-between interaction), assuming an effect size f of 0.245 (eta squared=0.06; estimated from data and equivalent to means differences >2.4), α error 0.05, β error 0.20, two groups (nebulization system), three measurements (pre, during, post) and a partial correlation (between measurements adjusting by patient) of 0.3. Values of $p < .05$ were considered to be statistically significant. Statistical analyses were performed using statistics software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc).

RESULTS

A total of 113 nebulizations were administered to 6 subjects, all of them were male and had moderate bronchiolitis, 7 points (8; 9) in bronchiolitis scale. The median [IQR] age and weight at admission was 1.5 months (1.0; 4.5) and 4.35 kg (2.85; 6.90), respectively. None of them had other underlying disease or factors of severity such as prematurity, cardiopathy, bronchopulmonary dysplasia, neuromuscular disease, immunodeficiency.

The comfort scales (CBS and VAS) assessed by health staff showed no differences between both methods of aerosol delivery, before and after the nebulization was given. During nebulization, comfort was greater with the NHF system compared to the JN: CBS scale (median [IQR]) was 10.7 (7;16) vs 14.5 (10;20) ($P = .006$) and VAS scale was 8.5 (6;10) vs 7 (4;9) ($P = .02$), respectively. Satisfaction assessed with the NRS scale during nebulization was greater with the NHF system compared to JN: 3.7 (3; 4) vs 2.5 (1; 4) ($P < .001$) (Fig. 2) (Table 1). Comfort scales assessed by parents during 26/113 nebulizations showed greater comfort and satisfaction with NHF compared to JN: CBS, VAS and NRS scores were 10.5, 9 and 4 vs 16.5, 4 and 2 for NHF and JN, respectively ($P < .05$) (Table 1). Correlation (Spearman´s rho) between CBS and VAS scale was -0.757 ($P < .001$). The intraclass correlation coefficient for CBS, VAS and NRS, measured by 2 different nurses was between 0.75 and 0.87.

There were no significant differences at baseline between the groups (NHF and JN) when analyzing the nebulized drug, time since last food intake, time of day (day time-night time), use of analgesia, oxygen saturation, breathing frequency, fraction of inspired oxygen and heart rate) (Table 2).

A significantly increased heart rate was registered in the JN and NHF groups during nebulization compared to the period before nebulization ($P < .05$), while there were no changes in oxygen saturation, breathing frequency and fraction of inspired oxygen.

DISCUSSION

In this randomized cross-over trial in infants with bronchiolitis, the levels of comfort and satisfaction during nebulization, detected by nurses and caregivers, were higher using a nebulizer integrated into HFNC than the standard nebulization with a JN connected to a face mask.

The advantages of HFNC, like the ease of setup, the adequate tolerance and minimal adverse events, have increased its use in pediatric care [27, 28]. The possibility of nebulization through HFNC and its differences to a JN have recently been demonstrated in various in vitro studies, including the pulmonary deposition and the nebulized particle size as determinants in the efficacy of this new system [19, 29]. However, clinical studies are lacking. To our knowledge, there is only one previous clinical study that compares these two methods of nebulization in a case series of 5 patients with bronchiolitis in a pediatric emergency department [22]. Our study contributes, in a randomized and controlled way, to assess the comfort with different validated medical scales, by not only health personnel but also by relatives, in children with bronchiolitis using a nebulization system integrated into HFNC compared with standard practice.

Family satisfaction has gained increasing interest as an important indicator of outcome in healthcare and for the evaluation of quality of care [30]. Young children with bronchiolitis cannot verbally express their level of satisfaction with treatment, with the opinion and satisfaction of caregivers being especially important. 'Satisfaction' refers to the amount of fulfillment of perceived or real, implicit or explicit needs and expectations of an individual or a group of persons. Thus it is a complex variable difficult to assess with no gold standard scale at hand [31-33]. Our results showed higher scores on NRS during the administration of aerosol therapy with NHF versus standard nebulization evaluated by nurses and caregivers.

Delivering aerosolized medication through a conventional device (JN) generates discomfort [12, 34]. It is important to point out that, according to our results, comfort levels are comparable with both devices before and after the nebulization, and it is during the actual use of the device that the NHF system is clearly superior to JN.

The COMFORT-B scale has gained a place in pediatric intensive care settings worldwide [35], and it has been used in hospitalized patients under 3 years of age [36]. With the aim of avoiding possible inter-

observer variability in scale punctuations, the CBS, VAS and NRS scores were assessed by two nurses; and we found a strong positive correlation between the two examiners. It is possible that the previous training of our health personnel may have influenced these good results, and reinforces the use of these scales as a measurement of comfort if they are assessed by qualified health personnel [37]. VAS has shown to be valid as a proxy measure recorded by an experienced person, such as a child´s caregiver [38, 39]. Importantly, as others have also reported, we found a strong association between VAS and CBS rating [36]. This association is extendable to the NRS satisfaction scale. Comfort and satisfaction can be understood as complementary variables that seek to express a similar objective: to evaluate the level of wellbeing of the patient.

One of the strengths of this study was the analysis of other variables that could have an influence on the results of comfort. In intensive care units greater discomfort has been described during the day compared to night time due to the presence of increased noise, number of health personnel, etc [40]. In our case, nebulization with each system was alternated, and day/night distribution was similar in both groups. Likewise, time since the last food intake, which also has an effect in comfort [41], was comparable in the two groups. Additionally, there were no differences in the use of analgesia, which was not needed in any of the groups [42]. In any case, the advantages of NHF system include avoiding discontinuation of respiratory support, promoting sleep [22] and liberating oral route to allow nebulization during feeding (breast feeding or oral eating) which may influence the course of the disease and reduce family stress [17, 43].

Our study has some limitations. First of all, the small number of patients included in this study decreases its external validity and we should be cautious when stablishing conclusions about the differences in comfort of the two nebulization methods between patients. However, the 113 measurements we obtained from those 6 patients, increases the power and precision of the estimations, by decreasing inter measurement variability. Secondly, we did not take into account other variables that could influence the comfort and satisfaction, such as the use of pacifiers or the administration of nebulizations in the parents' arms. On the other hand, although it was not the objective of this work, the study design could not research if delivering an aerosolized bronchodilator through HFNC may induce a significant clinical effect [19]. Our results showed comparable O2 need and O2 saturation

before and after the nebulization between both systems. We did find an increased heart rate during nebulization compared to previous baseline levels in the conventional JN system and NHF group. The clinical perception and the adequate comfort results obtained during nebulization with NHF suggest that the increase in HR may be mostly due to the chronotropic effect of the drugs, while in the case of the JN system the discomfort of the patient may also play a role. Morgan et al, described in a case series that HR increased to a greater degree with HFNC and the Aerogen Solo than with the jet nebulizer and face mask [22]. However, the aim of this study is not to recommend the use of nebulizations in this disease, but to encourage bearing the patients comfort in mind in case of doing it" and we insist that "further studies would be needed to consolidate such therapeutic efficacy.

CONCLUSIONS

Currently, bronchiolitis is a medical frustration, often with slow recovery and with a limited choice of therapeutic weapons. Ensuring comfort should be an intrinsic prerequisite to any treatment, especially if they have not demonstrated consistent efficacy.

HFNC is a frequently used respiratory support in this pathology, and aerosol therapy with a vibrating mesh nebulizer integrated into HFNC generates more comfort and satisfaction than the standard nebulization with a jet nebulizer connected to a face mask. Studies are necessary to demonstrate if this therapy improves the clinical course of this pathology.

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QUICK LOOK

Current knowledge

High-flow nasal cannula (HFNC) and aerosol therapy are part of the treatment for bronchiolitis. A jet nebulizer connected to a face mask is the most frequently used type of nebulizer, despite the controversy over its efficacy and poor tolerability, which generates discomfort in the child and stress in the whole family.

What this paper contributes to our knowledge

It is possible to increase the comfort of bronchiolitis patients with HFNC support who require nebulizations. Aerosol therapy with a nebulizer integrated in HFNC, compared to a traditional nebulizer, results in increased levels of patient comfort and satisfaction, measured with validated scales by both healthcare professionals and caregivers.

Figure Legends:

Figure 1.

Nebulizer system in patient with bronchiolitis and HFNC. **1A**, Aerogen nebulizer integrated in HFNC (NHF). **1B**, jet nebulizer with a face mask (JN).

Figure 2.

Repeated measures ANOVA's points of comfort (CBS, VAS) and satisfaction (NRS) measured by the health staff during the nebulization with NHF (solid line) showed greater comfort and satisfaction compared to JN (dashed line) during nebulization ($P < .001$)

CBS, COMFORT-behavior scale; VAS, visual analog scale; NRS, numeric rating scale.