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Humidified High Flow Nasal Cannula versus Nasal Continuous Positive Airway Pressure as an Initial Respiratory Support in Preterm Infants with Respiratory Distress: a Randomized, Controlled Non-Inferiority Trial

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Heated, humidified, high-flow nasal cannula (HHFNC) is frequently used as a noninvasive respiratory support for preterm infants with respiratory distress. But there are limited studies that compares HHFNC with nasal continuous positive airway pressure (nCPAP) only as the initial treatment of respiratory distress in preterm infants immediately after birth. The aim of this study is to assess the effectiveness and safety of HHFNC compared to nCPAP for the initial treatment of preterm infants with respiratory distress. Preterm infants at between 30 and 35 weeks of gestational age were randomized to HHFNC or nCPAP when they showed respiratory distress in less than 24 hours of age postnatally. Preterm infants who needed invasive respiratory supports were excluded. Primary outcome was the incidence of treatment failure (defined as need for the intubation or mechanical ventilation). Eighty-five infants were analyzed. Sixteen of 42 infants randomized to HHFNC showed treatment failure compared to 9 of 43 infants using nCPAP (Risk difference 17.17 [–1.90–36.23]; $P = 0.099$). In terms of the reason for treatment failure, the frequency of hypoxia was significantly higher in the HHFNC group than in the nCPAP group ($P = 0.020$). There was no difference between the 2 groups in terms of respiratory and clinical outcomes and complications. Although HHFNC is safe compared to nCPAP, it is not certain that HHFNC is effective compared to nCPAP non-inferiorly as an initial respiratory support in preterm infants with respiratory distress.

Keywords: High Flow Nasal Cannula; Continuous Positive Airway Pressure; Preterm Infants; Noninvasive Ventilation

INTRODUCTION

Non-invasive respiratory support, including nasal continuous positive airway pressure (nCPAP), was shown to be effective in treating infants in the initial phase of respiratory distress (1). Recently, heated, humidified high-flow nasal cannula (HHFNC) is frequently used as an alternative mode of noninvasive respiratory support in the neonatal intensive care unit. Because HHFNC has a simpler interface with the infant and smaller prongs than nCPAP, the cannula is perceived as easier to use, more comfortable for the infant, and advantageous for mother-infant bonding (2).

Recent Cochrane review of HHFNC use in preterm infants (3) concluded that HHFNC is effective as other forms of non-invasive respiratory support in preterm infants for preventing treatment failure, death and chronic lung disease. But these results were from the evidence for the use of HHFNC as a post-extubation support. Although some randomized trial (4,5) support the notion that HHFNC is as effective as nCPAP in the early stages of respiratory distress syndrome of newborn (RDS), the evidence for HHFNC for the primary treatment of RDS is still insufficient. The aim of this study was to assess the clinical effectiveness and safety of HHFNC compared to nCPAP as a noninvasive respiratory support for the initial respiratory management of respiratory distress in preterm infants.

MATERIALS AND METHODS

We conducted a randomized study in 87 preterm infants, who were admitted to a tertiary care neonatal intensive care unit (NICU) of Korea University Medical Center Ansan Hospital, Ansan city, Korea from August 2010 to August 2013, and were delivered at more than 30 weeks and less than 35 weeks of gestational age (Fig. 1).

Preterm infants who did not meet the invasive respiratory support (intubation and positive pressure ventilation) criteria

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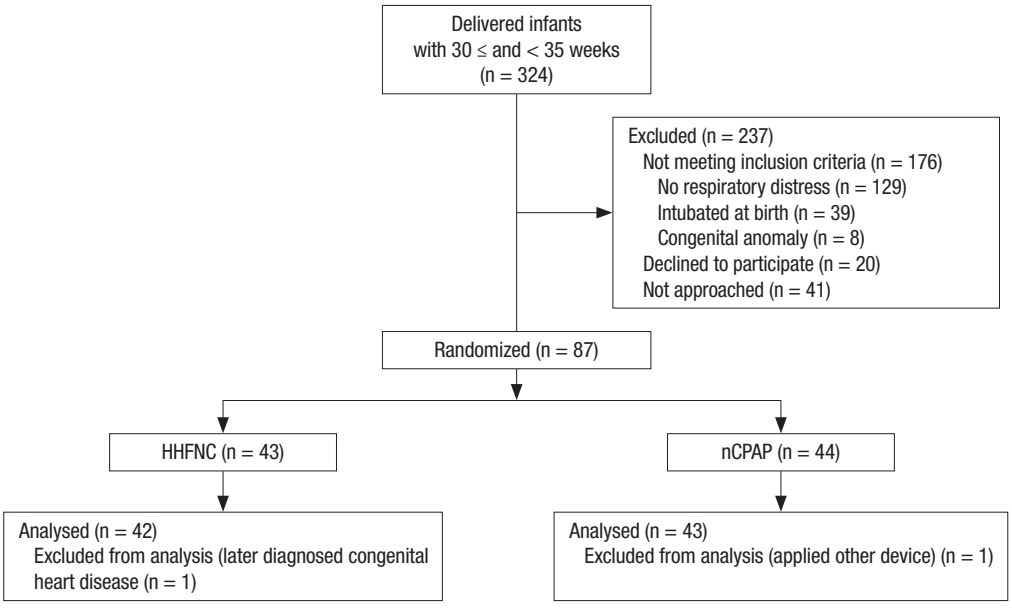

Fig. 1. Flowchart for describing enrollment.
HHFNC = heated, humidified, high flow nasal cannula, nCPAP = nasal continuous positive airway pressure.

after birth, but required non-invasive respiratory support for respiratory distress within 24 hours after birth were enrolled in this study. Preterm infants less than 30 weeks of gestational age or infants weighted 1,250 g or under at birth were excluded from this study because they were usually given prophylactic surfactant via an endotracheal tube in the delivery room or operation room. Infants were resuscitated according to the guidelines of the Neonatal Resuscitation Program.

The non-invasive respiratory support criteria were defined as follows: clinical signs of respiratory distress characterized by retraction, moaning sound and/or nasal flaring, pH < 7.25 and/or partial pressure carbon dioxide (pCO_2) > 65 mmHg, apnea (≥ 4 episodes/hour or need for mask ventilation ≥ 1 times/hour) and need for additional oxygen supply for maintenance of peripheral oxygen saturation (SpO_2) of 88%–94%. And, invasive respiratory support criteria after birth were defined as need for prolonged positive pressure ventilation during neonatal resuscitation at birth.

Infants with congenital anomalies of the upper airway tract, major congenital or chromosomal abnormalities, presence of air leak or cardiovascular instability, and infants whose parents did not provide consent or refused to allow their participation before randomization were excluded.

Study intervention

Randomization was performed by using random-number, computer-generated randomization (Excel; Microsoft Corp., Redmond, WA, USA), and sequentially numbered sealed opaque envelopes that contained the group assignments were prepared. When the infants were admitted to the NICU and had fulfilled the inclusion criteria, the envelopes were opened. The allocated treatment, HHFNC or nCPAP, was started immediately. The assigned mode of support was continued until the infant was ready to be placed in room air.

HHFNC

HHFNC support was delivered using the Optiflow System (Fisher & Paykel Optiflow System, Healthcare, Auckland, New Zealand). We used the short binasal prongs as interface with different sizes according to weight. Infants on HHFNC received a flow of 5 L/min initially and it was adjusted between 3–7 L/min according to the infant's respiratory condition (to ensure blood gas analysis results within normal ranges). A fraction of inspired oxygen (FiO_2) of 0.4 was initiated and it was adjusted until SpO_2 of 88%–94% was maintained. Weaning was started with a progressive reduction of the set FiO_2 (minimum 0.25), followed by a reduction of the flow to 3 L/min and then a reduction of FiO_2 to 0.21.

nCPAP

nCPAP was provided by the Infant Flow CPAP system (in CPAP mode only, not for BiPAP; CareFusion, Yorba Linda, CA, USA) or Millennium ventilator (Sechrist Industries, Inc., Anaheim, CA, USA) using short binasal prongs with different sizes according to weight. Infants on nCPAP received positive end expiratory pressure (PEEP) of 5 cmH_2O initially and it was adjusted between 4–7 cmH_2O according to the infant's respiratory condition (to ensure blood gas analysis results within normal ranges). FiO_2 of 0.4 was initiated and it was adjusted until SpO_2 of 88%–94% was maintained. Weaning was started with a progressive

reduction of the set FiO_2 (minimum 0.25), followed by a reduction of the PEEP to 4 cmH_2O and then a reduction of FiO_2 to 0.21.

Weaning

Respiratory supports were stopped when the infants showed no signs of respiratory distress with room air and SpO_2 > 88%, PCO_2 < 60 mmHg with FiO_2 of 0.21 and HHFNC flow rate of 3 L/min or nCPAP PEEP of 4 cmH_2O.

Treatment failure

Once an infant reached the following criteria for treatment failure, intubation and mechanical ventilation were started. Criteria for treatment failure included any of the following: respiratory acidosis ($PaCO_2$ > 65 mmHg with pH < 7.2 at maximum setting of the allocated device [flow 7 L/min or PEEP 7 cmH_2O]), hypoxia (FiO_2 > 0.4 to maintain SpO_2 88 to 94%) or apnea (> 2–3 episodes of apnea/hour requiring repeated stimulation or bag-and-mask ventilation) despite adequate prong fixation and flow or PEEP delivery.

Although an infant meets the above criteria, application of other type of non-invasive respiratory support device (from HHFNC to nCPAP and from nCPAP to Bilevel CPAP) was considered when the physician decided that the patient did not need to be intubated on a limited basis. This process reflected the clinical practice at many centers where these treatments are commonly available.

Outcomes

Newborns were monitored by SpO_2 monitoring. For each infant, the following variables were recorded; gestational age, birth weight, gender, mode of delivery, maternal obstetric history, and the Apgar scores at 1 and 5 minutes. At study entry, the main suspected causes of respiratory distress were recorded including RDS, apnea, transient tachypnea of newborn, pneumonia, or spontaneous pneumothorax. When it was difficult to distinguish the cause, we determined it based on the chest X-ray findings.

The primary outcome was the incidence of treatment failure with these 2 non-invasive respiratory support devices. Secondary outcomes were incidence of invasive ventilation, weaning rate by the time, duration of total respiratory support, incidence of air leak or nasal trauma, occurrence of respiratory distress syndrome treated with surfactant, bronchopulmonary dysplasia (BPD), incidence of symptomatic patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH, ≥ grade III), periventricular leukomalacia (PVL), bacteremia, necrotizing enterocolitis (NEC, ≥ stage 2), caffeine use, and days to full enteral feeds. BPD was defined according to the National Institutes of Health consensus definition (6), PDA was confirmed by echocardiography and symptomatic PDA was defined as PDA requiring pharmacological or surgical treatment. IVH was classified according to Papile et al. (7), and PVL as described by De Vries et al. (8). NEC was classified according to Bell's classification, modified by Kliegman and Walsh (9).

Statistical analysis

For the calculation of sample size, we used the incidence of treatment failure from allocated devices as the main primary outcome. We estimated that the initial respiratory support would have a failure rate of 16% for preterm babies on the basis of a review of the recent 2 years of data from our unit. We prespecified the margin of noninferiority for high flow nasal cannula as 20 percentage points above the failure rate for nCPAP (10). At a confidence level $\alpha = 0.05$ and power level of 0.80, we needed 42 patients in each group.

All analyses were performed on per-protocol basis, and infants remained in their assigned groups for analysis of all outcomes. For the primary outcome, we calculated risk difference and 95% confidence intervals (CIs). We used the χ^2 test or Fisher exact test to compare categorical variables and the appropriate parametric test (Student's t-test) or nonparametric test (Mann-Whitney U 2-sided tests) to compare continuous variables. A P value below 0.05 was considered statistically significant. All analyses were performed with the use of SPSS version 20 (IBM SPSS, Armonk, NY, USA).

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Korea University Ansan Hospital (Reg. No. AS 10046). Written informed consent was obtained during the first hour of life from the parents of the patients before enrollment in this study.

RESULTS

The baseline demographic characteristics of enrolled infants were similar between the 2 groups in terms of gestational age, birth weight, gender, incidence of cesarean delivery, occurrence of multiple pregnancies, premature rupture of membranes, administrations of antenatal glucocorticoid prophylaxis, incidence of preeclampsia, abruptio placenta, Apgar scores at 1 and 5 minutes, and the cause of respiratory distress (Table 1). There was no significant difference in terms of the main suspected causes of respiratory distress between the 2 groups (HHFNC, RDS 66.7% and transient tachypnea of the newborn [TTN] 31.0% vs. nCPAP, RDS 81.4% and TTN 18.6%; P = 0.228).

Primary outcome

The risk difference comparing the treatment failure rate between the nCPAP and HHFNC groups was 17.17 percentage points (95% CI, –1.90–36.23), which crossed the margin of the boundary of 20%. It is not certain that HHFNC is non-inferior to nC-

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Table 1. Perinatal characteristics of HHFNC and nCPAP groups

Characteristics	HHFNC (n = 42)	nCPAP (n = 43)	*P* value*
Gestational age, wk	32.5 ± 1.5	33.0 ± 1.2	0.255
Birth weight, g	2,058 ± 371	1,996 ± 374	0.446
Male gender	23 (54.8)	24 (55.8)	> 0.999
C/sec delivery	30 (71.4)	26 (60.5)	0.362
Twin	7 (16.7)	12 (27.9)	0.299
PROM	21 (50.0)	17 (39.5)	0.386
Antenatal steroid	27 (64.3)	23 (53.5)	0.380
Preeclampsia	8 (19.0)	5 (11.6)	0.382
GDM	2 (2.8)	3 (7.0)	0.511
Placenta abruption	4 (9.5)	5 (11.6)	0.515
1 min Apgar score	7 (6–8)	7 (5–8)	0.689
5 min Apgar score	9 (8–9)	9 (8–9)	0.679
Cause of respiratory distress			
Respiratory distress syndrome	28 (66.7)	35 (81.4)	0.228
Transient tachypnea of newborn	13 (31.0)	8 (18.6)	
Others (apnea, unclassified)	1 (2.4)	0	

Values are expressed as mean ± standard deviation or median (IQR) for continuous variables, as number (%) for categorical variables.
HHFNC = heated, humidified, high flow nasal cannula, nCPAP = nasal continuous positive airway pressure, C/sec = Cesarean section, PROM = premature rupture of membrane, GDM = gestational diabetes mellitus, IQR = interquatile range.
*P values were calculate by the χ^2 test, the Fisher exact test or Mann-Whitney U 2-sided test.

Table 2. Primary outcome for infants assigned to receive either HHFNC or nCPAP for the initial respiratory support

Outcomes	HHFNC (n = 42)	nCPAP (n = 43)	Risk difference (95% CI)* percentage points	*P* value†
Treatment failure	16 (38.1)	9 (20.9)	17.17 (–1.90–36.23)	0.099
Reasons				
Hypoxia	15 (35.7)	6 (14.0)	-	0.020
Respiratory acidosis	2 (4.8)	4 (9.3)	-	0.676
Additional management				
Endotracheal intubation	13 (31.0)	8 (18.6)	13.17 (–4.72–31.07)	0.216
Noninvasive devices	3 (7.1)	1 (2.3)	4.82 (–4.18–13.82)	0.360

Values are expressed as number (%) for categorical variables.
HHFNC = heated, humidified, high flow nasal cannula, nCPAP = nasal continuous positive airway pressure, CI = confidence interval.
*Positive values favor the nCPAP group, and negative values favor the HHFNC group; †*P* values were calculated by the χ^2 test or the Fisher exact test.

Table 3. Outcomes including weaning rate by the time, period needed respiratory support and respiratory outcomes

Outcomes	HHFNC (n = 42)	nCPAP (n = 43)	*P* value*
Weaned from the assigned device†	26 (61.9)	34 (79.1)	0.099
Rate by the time†			
Within 24 hr	8 (19.0)	10 (23.3)	0.635
Within 48 hr	12 (28.6)	17 (39.5)	0.286
Within 72 hr	20 (47.6)	27 (62.8)	0.104
Within 7 day	26 (61.9)	32 (74.4)	0.215
7 days–	26 (61.9)	34 (79.1)	0.082
Using the assigned device	49.5 (23.8–70.3)	47.5 (23.3–65.6)	0.923
Total respiratory support	67 (40.0–106.8)	52 (34.0–88.0)	0.179
RDS treated with surfactant	12 (28.6)	7 (16.3)	0.201
Bronchopulmonary dysplasia	1 (2.4)	0 (0.0)	-
Air leak	2 (4.8)	0 (0.0)	-

Values are expressed as median (IQR) for continuous variables, as number (%) for categorical variables.
HHFNC = heated, humidified, high flow nasal cannula, nCPAP = nasal continuous positive airway pressure, RDS = respiratory distress syndrome of newborn, IQR = interquatile range.
*P values were calculated by the χ^2 test, the Fisher exact test or Mann-Whitney U 2-sided test; †Cumulative number of patients (%) weaned from the allocated ventilators.

Table 4. Clinical outcomes associated with caring preterm infants

Clinical outcomes	HHFNC (n = 42)	nCPAP (n = 43)	*P* value*
Symptomatic PDA	7 (16.7)	2 (4.7)	0.073
IVH (grade ≥ III)	0 (0.0)	0 (0.0)	-
PVL	0 (0.0)	1 (2.3)	0.506
Bacteremia	0 (0.0)	0 (0.0)	-
NEC (stage ≥ 2)	0 (0.0)	0 (0.0)	-
Apnea, treated with caffeine	11 (26.2)	9 (20.9)	0.616
Total parenteral nutrition	7 (16.7)	4 (9.3)	0.351
Time to full feeds from birth, day	6 (5.0–9.5)	6 (5.0–9.0)	0.470
Time to full oral feed, day	14 (7–23)	13 (6–23)	0.651
Length of stay, day	20 (15.8, 28.3)	21 (16.0, 32.0)	0.765

Values are expressed as median (IQR) for continuous variables, as number (%) for categorical variables.
HHFNC = heated, humidified, high flow nasal cannula, nCPAP = nasal continuous positive airway pressure, PDA = patent ductus arteriosus, IVH = intraventricular hemorrhage, PVL = periventricular leukomalacia, NEC = necrotizing enterocolitis, IQR = interquatile range.
*P values were calculated by the χ^2 test, the Fisher exact test or Mann-Whitney U 2-sided test.

PAP although the difference was not significant (HHFNC, 38.1% vs. nCPAP, 20.9%; P = 0.099) (Table 2).

The reasons for treatment failure were hypoxia (HHFNC, n = 15; nCPAP, n = 6) and respiratory acidosis (HHFNC, n = 2; nCPAP, n = 4). In terms of the reason for treatment failure, the frequency of hypoxia was significantly higher in the HHFNC group than in the nCPAP group (P = 0.020). Most infants who showed treatment failure with the assigned ventilator were finally intubated (HHFNC, 31.0% vs. nCPAP 18.6%; P = 0.216). One patient was intubated urgently because of development of tension pneumothorax. Three infants in the HHFNC group who met the treatment failure criteria were switched to nCPAP and 1 infant in the nCPAP group who met the treatment failure criteria was switched to Bilevel CPAP as a rescue therapy. They recovered from respiratory distress without intubation and mechanical ventilation.

Respiratory outcomes

The number of infants who recovered from respiratory distress with HHFNC was less than the number of infants who recovered from respiratory distress with nCPAP; however, there was no statistically significant difference between the 2 groups (62.9% vs. 79.1%, respectively; P = 0.099) (Table 3). Weaning rate from the assigned device by the time and the duration of using the assigned devices in case of success did not differ between the studied groups. Also, the duration of total respiratory support between the 2 groups was not significantly different (HHFNC, 67 [40–106.75] hours vs. nCPAP, 52 [34–88] hours; P = 0.179). In

term of the respiratory outcome, no significant differences were found between the 2 groups in terms of the need for surfactant and developments of BPD and air leak.

Complications

Air leak occurred in 2 cases of the HHFNC group and 1 of them was intubated because of pneumothorax. During this study period, there were no cases of injury to the nasal septum (redness, excoriation, bleeding, or crusting) due to nasal prongs.

Clinical outcomes

There were no significant differences in the incidence of symptomatic PDA, IVH, PVL, bacteremia, NEC, time to full enteral feeding from birth or length of hospital stay (Table 4).

DISCUSSION

This trial intended to assess the noninferiority of HHFNC as compared with nCPAP for the initial treatment of respiratory distress in preterm infants (30 ≤ and < 35 weeks of gestational age). It is not certain that HHFNC is non-inferior to nCPAP although the difference was not significant (11). A few randomized, controlled prospective studies have compared HHFNC with nCPAP (4,5,12). One of the studies compared HHFNC with nCPAP for treatment of early respiratory distress or post-extubation of preterm infants (12). But, this study did not analyze the results of indications separately. This study exhibited similar efficacy and safety between HHFNC and nCPAP overall. Other studies compared HHFNC with nCPAP for the treatment of RDS, and they showed similar efficacy between 2 groups (4,5). Although these results support for the use of HHFNC as an initial mode of ventilation in infants with respiratory distress, the evidence for HHFNC for the primary treatment of RDS is still insufficient. In our study, infants with respiratory distress after birth (who needed initial respiratory support) were recruited into the study, and infants who did well on the assigned mode were not exposed to endotracheal ventilation or surfactant.

HHFNC and nCPAP act physiologically differently and need to be set accordingly in a different manner. HHFNC was not designed originally to deliver PEEP, but to washout the anatomical and physiological dead space. This results in improving gas exchange and decreasing the work of breathing (13). When using nCPAP we occlude the nares to create a PEEP. But proper positioning of the nasal cannula to maintain an adequate seal is difficult in preterm infants and requires frequent adjustment. In contrast, HHFNC does not require a close fit of nasal prongs with nares. Ease of HHFNC use has helped to increase its popularity among preterm infants.

HHFNC probably create PEEP (14-16). HHFNC provides inspiratory support, and if the flow rate of the device exceeds the inspiratory flow rate generated by the patient, then there will be unquantified positive respiratory support during inspiration. During expiration, the patient has to expire air against the high flow and PEEP may be generated depending on the size of the leak (17). This concept would theoretically lead us to assume that HHFNC could supports functional residual capacity during in the initial treatment of respiratory distress of preterm infants. But, limited evidence is available about the use of HHFNC as an initial mode of ventilation in infants with respiratory distress.

Our study included only preterm infants between 30 and 35 weeks of gestational age. Hence, we cannot generalize this finding to other smaller preterm infants, or infants presenting with more severe respiratory distress. We assume that the use of HHFNC as an initial treatment would not be suitable for treatment of initial respiratory distress in smaller preterm infants although there was no significant difference in the incidence of RDS treated with surfactant between the 2 groups.

In the initial phase of RDS or TTN, uneven ventilation is common and the infants experience respiratory distress and increased work of breathing. Thus, the risk of air leak is relatively high. Because pressures were not monitored during HHFNC, there was a concern of increased risk of air leak. One of our enrolled patients was intubated because of development of pneumothorax during support by HHFNC. However, in the previous studies, the incidence of air leak was very low after HHFNC and nCPAP (< 1% vs. 2% in the study by Yoder et al. [12], 0% vs. 2% in the study by Collins et al. [18] and 0% vs. 0.7% in the study by Manley et al. [10]) for early treatment and post-extubation.

Nasal trauma can occur after nCPAP (19). However, we did not encounter a case of nasal trauma in both groups. This discrepancy could be due to the different nature of the studies, in which we treated the initial phase of respiratory distress and provide support for a shorter period. Also, the gestational age of infants in our study were older compared to that in other studies (10,18). Less trauma could be due to different routines of nasal prongs handling and fixation.

Our study limitation is that randomized mode of support could not be blinded to the medical team. Although we used the objective failure criteria and management protocols, the possibility of a bias might exist. Also, as there was no previous study on the initial treatment with HHFNC, determination of margin of noninferiority for the statistical analysis was somewhat arbitrary. Therefore, the sample size of this study may not have been large enough to compare the effectiveness between the 2 devices.

We conclude that there is no evidence to support the noninferiority of HHFNC compared to nCPAP as an initial management of respiratory distress in premature infants at between 30 and 35 weeks gestational age. The difference in failure rate is not significant without an increase in the incidence of complications; further randomized controlled studies are required to assess the effectiveness and safety of HHFNC as an initial treat-

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ment in preterm infants with respiratory distress.

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DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Park K, Choi BM. Investigation: Shin J, Park K, Choi BM. Data curation: Shin J, Lee EH. Formal analysis: Shin J, Lee EH. Writing - original draft: Shin J, Choi BM.

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